FILE 'REGISTRY' ENTERED AT 16:06:38 ON 12 FEB 2003
L1 STRUCTURE UPLOADED
L2 0 S L1 FUL
L3 STRUCTURE UPLOADED
L4 0 S L3 FUL
L5 STRUCTURE UPLOADED
L6 91 S L5 FUL
L7 88 S L6 AND CAPLUS/LC
L8 3 S L6 NOT L7
L9 STRUCTURE UPLOADED
L10 0 S L9 FUL

FILE 'CAPLUS' ENTERED AT 16:10:17 ON 12 FEB 2003

=> s l6
L11 62 L6

=> d 1-62 ibib abs hitstr

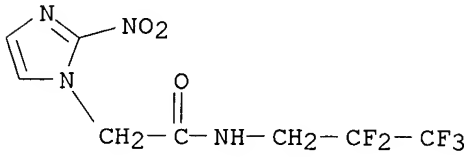
L11 ANSWER 1 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:526269 CAPLUS
DOCUMENT NUMBER: 137:292513
TITLE: Effects of hyperglycemia on oxygenation, radiosensitivity and bioenergetic status of subcutaneous RIF-1 tumors
AUTHOR(S): Nadal-Desbarats, L.; Poptani, H.; Oprysko, P.; Jenkins, W. T.; Busch, T. M.; Nelson, D. S.; Glickson, J. D.; Koch, C. J.; Evans, S. M.
CORPORATE SOURCE: Department of Radiology, University of Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: International Journal of Oncology (2002), 21(1), 103-110
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Since tissue O tension is a balance between delivery and consumption of O, considerable effort was directed at increasing the former and/or decreasing the latter. Techniques to decrease the rate of cellular O consumption (increasing the distance O can diffuse into tissues) include increasing glycolysis by administering supraphysiol. levels of glucose. We have examd. the effect of hyperglycemia produced by i.v. glucose infusion on the tissue oxygenation and radiation response of s.c. implanted murine radiation induced fibrosarcomas (RIF-1). A 0.3 M glucose soln. was delivered via tail vein injection according to a protocol that maintained glucose at a plasma concn. of 17.+-.1 mM. The effect of this treatment on radiation response (clonogenic and growth delay studies), tumor oxygenation (needle electrode pO2 and 2-[2-nitro-1H-imidazol-1-yl]-N-(2,2,3,3,3-pentafluoropropyl) acetamide (EF5) binding), and tumor bioenergetics and pH (31P NMR spectroscopy) was examd. Systemic measurements included hematocrit and blood glucose and lactate concns. The results of these studies suggest that these s.c. implanted RIF-1 tumors are both radiobiol. and metabolically hypoxic and that i.v. glucose

infusion is not an effective method of modifying this metabolic state.

IT **152721-37-4**, EF5
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(hyperglycemia effect on oxygenation, radiosensitivity, and EF5 binding
in s.c. RIF-1 tumors)

RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)

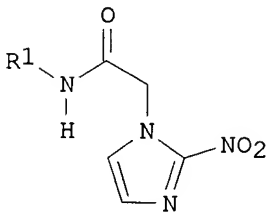


L11 ANSWER 14 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:78365 CAPLUS
DOCUMENT NUMBER: 134:147601
TITLE: Preparation of fluorinated nitroimidazole compounds and their labeled counterparts for the detection of hypoxia
INVENTOR(S): Dolbier, William R.; Li, An-Rong; Koch, Cameron J.; Kachur, Alexander V.
PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania, USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007414	A1	20010201	WO 2000-US40437	20000720
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1202973	A1	20020508	EP 2000-960168	20000720
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

PRIORITY APPLN. INFO.: US 1999-144747P P 19990721
WO 2000-US40437 W 20000720

GI



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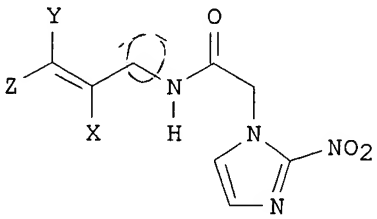

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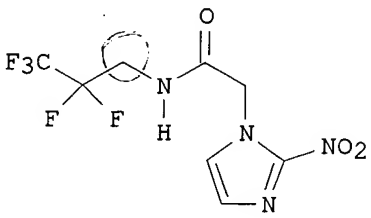

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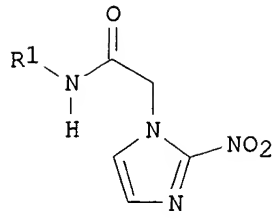

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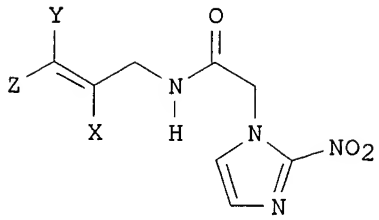

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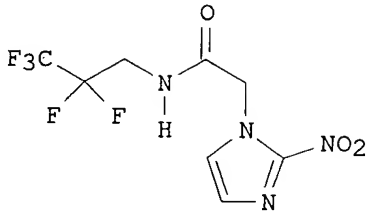


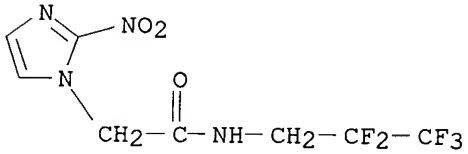
III

AB Methods for prepg. novel fluorinated nitroimidazoles I [R1 = CH2CHFCH2F, CH2CHFCHF2, CH2CHFCF3, CH2CH2CH2F, CH2CF2CHF2, and CH2CF2CF3], their 18F-labeled counterparts [at least one F is 18F], along with their corresponding intermediates II [X, Y, and Z are independently H or F] are disclosed. Thus, III (EF5) was prepd. by fluorination of the allyl precursor 2-(2-nitro-1H-imidazol-1-yl)-N-(2,3,3-trifluoroallyl)acetamide (II; X = Y = Z = F). The title compds. are disclosed as agents for non-invasive imaging techniques, such as PET, for detecting tissue hypoxia and demonstrated in PET imaging of a tumor-bearing rat treated with [18F]-labeled EF5. Diagnostic kits useful in practicing the methods of claimed invention are also provided.

IT **152721-37-4P 322637-51-4P 322637-52-5P 322637-53-6P 322637-54-7P 322637-55-8P 322637-56-9P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of fluorinated nitroimidazoles and their labeled counterparts as medical imaging agents for the detection of hypoxia)

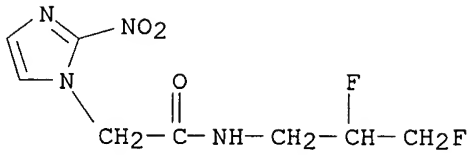
RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)

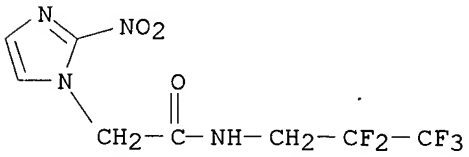


RN 322637-51-4 CAPLUS

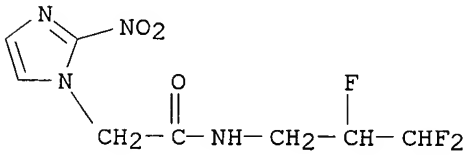
CN 1H-Imidazole-1-acetamide, N-(2,3-difluoropropyl)-2-nitro-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



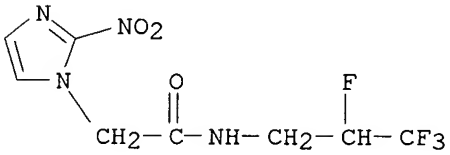
RN 322637-52-5 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



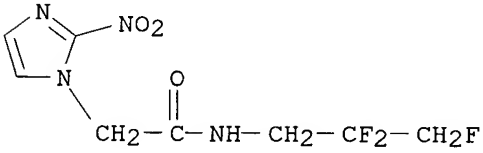
RN 322637-53-6 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,3,3-trifluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



RN 322637-54-7 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,3,3,3-tetrafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)

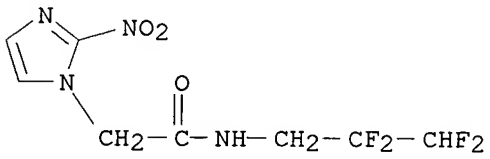


RN 322637-55-8 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3-trifluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



RN 322637-56-9 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3-tetrafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 15 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:806871 CAPLUS
DOCUMENT NUMBER: 134:207753
TITLE: [18F]-EF5, a marker for PET detection of hypoxia: synthesis of precursor and a new fluorination procedure
AUTHOR(S): Dolbier, W. R.; Li, A.-R.; Koch, C. J.; Shiue, C.-Y.; Kachur, A. V.
CORPORATE SOURCE: Department of Chemistry, University of Florida, Gainesville, FL, 32611, USA
SOURCE: Applied Radiation and Isotopes (2000), Volume Date 2001, 54(1), 73-80
CODEN: ARISEF; ISSN: 0969-8043
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:207753

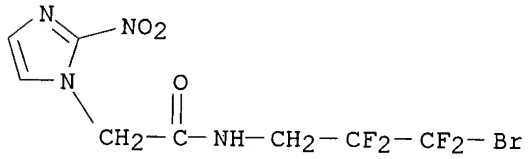
AB There is a great deal of clin. and exptl. interest in detg. tissue hypoxia using non-invasive imaging methods. The authors have previously developed EF5, 2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide, with both invasive and non-invasive hypoxia detection in mind. EF5 and other 2-nitroimidazoles are used to detect hypoxia, because the rate of their bioreductive metab. is inversely dependent on oxygen partial pressure. Such metab. leads to the formation of covalent adducts within the metabolizing cells. Previously, the authors have described the invasive detection of these adducts by highly specific monoclonal antibodies after tissue biopsy. In this work, the authors synthesized 18F-labeled EF5, [18F]-2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide, in greater than 10% yield by direct fluorination of the newly synthesized precursor 2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,3,3-trifluoroallyl)acetamide by [18F]-F2 in trifluoroacetic acid. The objective was to optimize the electrophilic fluorination of the fluorinated alkene bond with fluorine gas, a new method of 18F-labeling of polyfluorinated mols. Previous biodistribution studies in mice have demonstrated uniform access of EF5 to all tissues with bioelimination dominated by renal excretion. When [18F]-EF5 was injected into a rat followed by urine collection and anal., the authors found no detectable metab. to other radioactive compds. Thus,

[18F]-EF5 should be well suited for use as a non-invasive hypoxia marker with detection using positron emission tomog. (PET).

IT **328386-75-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(using electrophilic fluorination in acidic medium to prep. [18F]-EF5, marker for PET detection of hypoxia)

RN 328386-75-0 CAPLUS

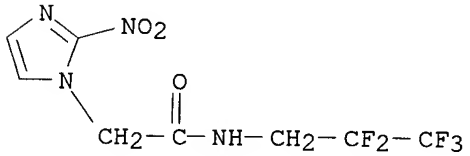
CN 1H-Imidazole-1-acetamide, N-(3-bromo-2,2,3,3-tetrafluoropropyl)-2-nitro- (9CI) (CA INDEX NAME)



IT **152721-37-4P**, EF5
RL: SPN (Synthetic preparation); PREP (Preparation)
(using electrophilic fluorination in acidic medium to prep. [18F]-EF5, marker for PET detection of hypoxia)

RN 152721-37-4 CAPLUS

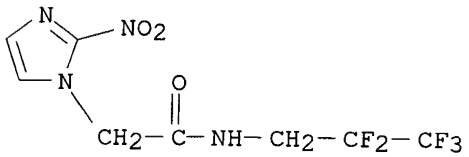
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)



IT **322637-52-5P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(using electrophilic fluorination in acidic medium to prep. [18F]-EF5, marker for PET detection of hypoxia)

RN 322637-52-5 CAPLUS

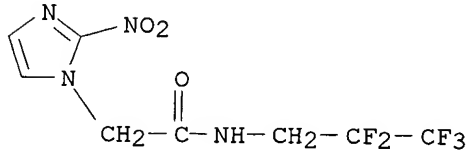
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 16 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:248505 CAPLUS
DOCUMENT NUMBER: 133:29066
TITLE: Detection of hypoxia in human squamous cell carcinoma by EF5 binding
AUTHOR(S): Evans, Sydney M.; Hahn, Stephen; Pook, Deirdre R.; Jenkins, W. Timothy; Chalian, Ara A.; Zhang, Paul; Stevens, Craig; Weber, Randall; Weinstein, Gregory; Benjamin, Ivor; Mirza, Natasha; Morgan, Mark; Rubin, Steven; McKenna, W. Gillies; Lord, Edith M.; Koch, Cameron J.
CORPORATE SOURCE: Schools of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: Cancer Research (2000), 60(7), 2018-2024
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Localization and quantitation of 2-nitroimidazole drug binding in low pO2 tumors is a technique that can allow the assessment of hypoxia as a predictive assay. EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide] is such a drug, and it has been shown to be predictive of radiation response in rodent tumors. Using fluorescence immunohistochem. techniques, data on the presence, distribution, and levels of EF5 binding as a surrogate for hypoxia in human head and neck and uterine cervix squamous-cell cancers (SCCs) are provided. Six patients with SCC were studied. Four patients had head and neck tumors, and two had uterine cervix cancers. The incubation of fresh tissue cubes in EF3 under hypoxic conditions ("ref. binding") demonstrated that all tumors were capable of binding drug, and that this binding varied by a factor of 2.9-fold (174.5-516.1) on an abs. fluorescence scale. In the five patients treated at the lowest drug doses (9 mg/kg), in situ binding was quantifiable. For all six patients, the max. rate of in situ binding varied by a factor of 6.7 between the lowest and highest binding tumor (24.8-160.3) on an abs. fluorescence scale. In tumors with high binding regions, intratumoral heterogeneity was large, extending from minimal fluorescence (<1%) up to 88.6% of ref. binding. In tumors with minimal binding, there was little intratumoral heterogeneity. These studies demonstrate substantial heterogeneity of in situ binding between and within individual squamous-cell tumors.
IT **152721-37-4**, EF5
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(detection of hypoxia in human squamous-cell carcinoma by EF5 binding)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)



L11 ANSWER 13 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:113367 CAPLUS
DOCUMENT NUMBER: 135:134082
TITLE: Hypoxia in human intraperitoneal and extremity sarcomas
AUTHOR(S): Evans, S. M.; Hahn, S. M.; Magarelli, D. P.; Zhang, P. J.; Jenkins, W. T.; Fraker, D. L.; Hsi, R. A.; McKenna, W. G.; Koch, C. J.
CORPORATE SOURCE: From the School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA, USA
SOURCE: International Journal of Radiation Oncology, Biology, Physics (2001), 49(2), 587-596
CODEN: IOBPD3; ISSN: 0360-3016
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The presence of hypoxia, measured by needle electrodes, was shown to be assocd. with poor patient outcome in several human tumor types, including soft tissue sarcomas. The present report emphasizes the evaluation of hypoxia in soft tissue sarcomas based upon the binding of the 2-nitroimidazole drug EF5 (2-{2-nitro-1H-imidazol-1-yl}-N-(2,2,3,3,3-pentafluoropropyl) acetamide). EF5 has previously been shown to be predictive of radiation response in animal tumors and in in vitro studies.

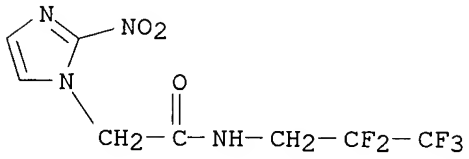
The authors have also previously reported studies of EF5 binding in human squamous cell tumors. Using fluorescent immunohistochem. techniques, the authors provide data on the presence and distribution of EF5 binding, as a surrogate for hypoxia, in human spindle cell tumors. Patients with spindle cell tumors who were scheduled for tumor surgery were asked to participate in the phase I trial of EF5. Approx. 48 h preoperatively, EF5 was administered i.v. at doses between 9 and 21 mg/kg. Binding in frozen sections of biopsied tissues was detd. using monoclonal antibodies labeled with the green-excited, orange-emitting fluorescent dye, Cy3. Calibration studies were performed in vitro by incubating fresh tumor tissue cubes obtained from each patient with EF3 (an analog of EF5) under hypoxic conditions ("ref. binding"). The goal of these calibration studies was to quantify the maximal binding levels possible in individual patient's tissues. The relationship between binding (in situ based on EF5 binding) and ref. binding (in vitro based on EF3 binding) was detd. 8 Patients were studied; 3 of these patients had gastrointestinal stromal tumors (GIST). The incubation of tumor tissue cubes in EF3 under hypoxic conditions demonstrated that all tumors bound drug to a similar extent. Ref. binding showed a 3.2-fold variation in median fluorescence (113-356) on an abs. fluorescence scale, calibrated by a Cy3 dye std. In situ binding in the brightest tumor section varied by a factor of 25.4 between the lowest and highest binding tumor (7.5-190.2). Heterogeneity of highest binding was greater between tumors than within individual tumors. A correspondence between EF5 binding and Eppendorf needle electrode studies was seen in the 5 patients with non-GISTs. Inter- and intratumoral heterogeneity of EF5 binding in spindle cell tumors was documented. Patterns of binding consistent with diffusion limited hypoxia

are present in human spindle cell neoplasms.

IT **152721-37-4**, EF5
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST
(Analytical study); BIOL (Biological study); USES (Uses)
(hypoxia anal. in sarcomas by immunohistochem. using EF5)

RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)



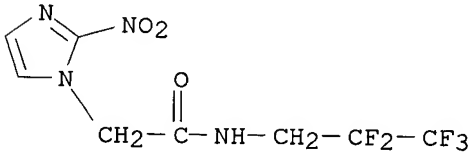
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:790212 CAPLUS
DOCUMENT NUMBER: 136:67942
TITLE: Hypoxia-inducible factor-1.alpha. is an intrinsic marker for hypoxia in cervical cancer xenografts
AUTHOR(S): Vukovic, Vojislav; Haugland, Hans Kristian; Nicklee, Trudey; Morrison, Andrew J.; Hedley, David W.
CORPORATE SOURCE: Departments of Medical Biophysics, Ontario Cancer Institute/Princess Margaret Hospital, Toronto, ON, M5G 2M9, Can.
SOURCE: Cancer Research (2001), 61(20), 7394-7398
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The hypoxia-inducible factor 1 (HIF-1) is known to induce the expression of several proteins linked to the maintenance of oxygen homeostasis, cellular energy metab., and tumor progression. Its .alpha. subunit (HIF-1.alpha.) is stabilized under hypoxic conditions and, therefore, might represent an intrinsic marker for tissue, hypoxia. Here we report on the spatial relationship between HIF-1.alpha. and the nitroimidazole hypoxia marker EF5 in cervical carcinoma xenografts, and on their spatial relationship to tumor blood vessels. EF5 was administered to mice bearing ME180 and SiHa cervical cancer xenografts. Frozen tumor tissue sections, triple-stained for HIF-1.alpha., the endothelial cell marker CD31, and EF5, were imaged using wide-field multiparameter immunofluorescence microscopy. Expression levels of EF5 and HIF-1.alpha. were similar in ME180 xenografts, but the percentage of tumor area stained with EF5 was significantly smaller than the percentage of HIF-1.alpha.-pos. area in SiHa tumors. In both tumor types the EF5-HIF-1.alpha. overlap was statistically significant, thus confirming their spatial and temporal colocalization. Spatial distribution anal. of EF5 and HIF-1.alpha. is consistent with different pO2 value "thresholds" for EF5 binding and HIF-1.alpha. expression. Summarized, our results indicate that HIF-1.alpha. is a useful intrinsic marker for hypoxia in cervical carcinoma xenografts.

IT **152721-37-4**
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(hypoxia-inducible factor-1.alpha. as intrinsic marker for hypoxia in cervical carcinoma xenografts)

RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)



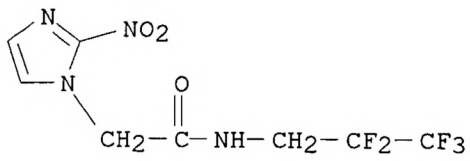
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L11 ANSWER 8 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:644457 CAPLUS
DOCUMENT NUMBER: 137:29877
TITLE: Pharmacokinetics of EF5 [2-(2-nitro-1-H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide] in human patients: implications for hypoxia measurements in vivo by 2-nitroimidazoles
AUTHOR(S): Koch, C. J.; Hahn, S. M.; Rockwell, K., Jr.; Covey, J. M.; McKenna, W. G.; Evans, S. M.
CORPORATE SOURCE: University of Pennsylvania School of Medicine, Radiation Oncology, Philadelphia, PA, 19104-6072, USA
SOURCE: Cancer Chemotherapy and Pharmacology (2001), 48(3), 177-187
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objectives: Pharmacokinetic studies were performed on the 1st 28 patients enrolled in a phase I trial to det. the ability of EF5 [2-(2-nitro-1-H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide] to detect hypoxia in human tumors in the absence of patient toxicity. Methods: EF5 was made in purified form and formulated for i.v. injection by the National Cancer Institute. After obtaining consent from the patients, EF5 was administered and blood samples were drawn at various times over approx. 48 h. For most patients it was possible to collect total urine at approx. 8-h intervals. EF5 in plasma and urine was analyzed by high-performance liq. chromatog. Results: EF5's blood plasma concn. followed a simple exponential decay following infusion. The plasma half-life was 11.7 h and was not affected by drug dose (9 to 28 mg/kg), fractional urine recovery, patient wt., or gender. Abs. plasma values suggested even biodistribution of the drug throughout the soft tissue with a vol. of distribution equal to 0.56 l/kg. Despite the relatively high lipid partition coeff. (logP=0.6), EF5 was excreted primarily (.ltoreq. 70%) via kidney clearance. No drug metabolites (e.g. retaining the 2-nitroimidazole chromophore) were detected in either plasma or urine. No toxicity was found at drug doses adequate to detect tumor hypoxia. Conclusions: Currently held paradigms of 2-nitroimidazole metab. (e.g. clearance rate and toxicity as affected by octanol/water partition coeff.) are discussed. The results reported herein suggest that EF5 is biol. stable with predictable pharmacokinetics. EF5's consistent half-life and clearance properties will allow quant. anal. of EF5 binding relative to tissue oxygen levels.

IT **152721-37-4**, EF5
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetics of EF5 in human cancer patients)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)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NO2
N
O
CH2 C NH CH2 CF2 CF3

L11 ANSWER 32 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:494670 CAPLUS
DOCUMENT NUMBER: 125:162343
TITLE: Detection of hypoxia with reagents containing 2-nitroimidazole compounds and methods of making such reagents
INVENTOR(S): Koch, Cameron J.; Lord, Edith M.
PATENT ASSIGNEE(S): The Trustees of the Univ. of Pennsylvania, USA; The University of Rochester
SOURCE: U.S., 29 pp., Cont.-in-part of U.S. Ser. No. 978,918,abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

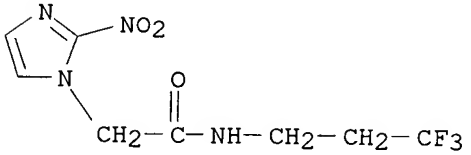
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5540908	A	19960730	US 1994-286065	19940804
CA 2149770	AA	19940526	CA 1993-2149770	19931118
US 5843404	A	19981201	US 1996-598752	19960208
US 6252087	B1	20010626	US 1998-123300	19980728

PRIORITY APPLN. INFO.: US 1992-978918 B2 19921119
US 1994-286065 A3 19940804
US 1996-598752 A2 19960208
OTHER SOURCE(S): MARPAT 125:162343

AB Novel nitroarom. compds. and immunogenic conjugates comprising a novel nitroarom. compd. and a carrier protein are disclosed. The invention further presents monoclonal antibodies highly specific for the claimed nitroarom. compds., protein conjugates of the compds., reductive byproducts of the compds., and adducts formed between the compds. and mammalian hypoxic cell tissue proteins. The invention is further directed to methods for detecting tissue hypoxia using immunohistol. techniques, noninvasive nuclear medicine methods (PET, SPECT), or NMR. Diagnostic kits useful in practicing the methods of claimed invention are also provided.

IT **180208-73-5P**
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(hypoxia detection with 2-nitroimidazole compds. and immunogenic conjugates)

RN 180208-73-5 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoropropyl)- (9CI) (CA INDEX NAME)

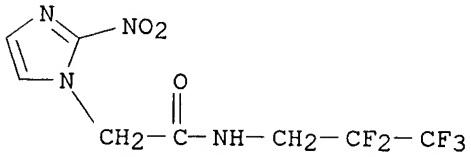


IT **152721-37-4P**

RL: ARG (Analytical reagent use); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hypoxia detection with 2-nitroimidazole compds. and immunogenic conjugates)

RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)



L11 ANSWER 33 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:492707 CAPLUS

DOCUMENT NUMBER: 125:185094

TITLE: Immunocytochemical labeling of aerobic and hypoxic mammalian cells using a platinated derivative of EF5

AUTHOR(S): Matthews, J.; Adomat, H.; Farrell, N.; King, P.; Koch, C.; Lord, E.; Palcic, B.; Poulin, N.; Sangulin, J.; Skov, K.

CORPORATE SOURCE: Department Medical Biophysics, BC Cancer Research Centre, Vancouver, BC, V5Z 1L3, Can.

SOURCE: British Journal of Cancer, Supplement (1996), 74(27), S200-S203
CODEN: BJCSB5; ISSN: 0306-9443

PUBLISHER: Stockton

DOCUMENT TYPE: Journal

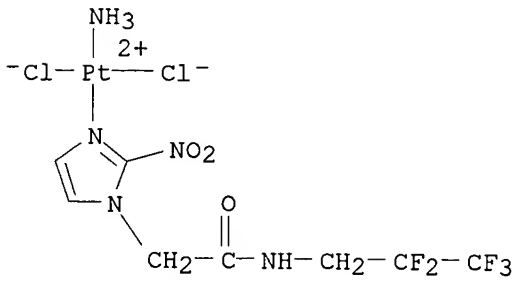
LANGUAGE: English

AB The monoclonal antibody ELK3-51 was previously developed to detect adducts of the 2-nitroimidazole EF5. Direct immunofluorescence was used to detect adducts of EF5 or of a platinated deriv. cis-[PtCl2(NH3)EF5] in SCCVII cells treated under aerobic or hypoxic conditions. Fluorescence measurements of these cells using both image and flow cytometric methods were compared, giving similar profiles. Platination significantly decreased immunofluorescence levels (.apprx.4-fold less than EF5) after 3 h in hypoxia, but also increased levels after exposure in air (.apprx.1.5 .times.) such that the hypoxic ratio decreased from .apprx.50 to .apprx.13. Platinated EF5 also showed significantly greater cytotoxicity than its parent in both aerobic and hypoxic cells. These results are consistent with targeting of EF5 to DNA, which was confirmed qual. by confocal microscopy.

IT **180990-37-8**
RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(immunocytochem. labeling of aerobic and hypoxic mammalian cells using a platinated deriv. of EF5)

RN 180990-37-8 CAPLUS

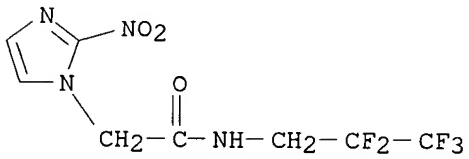
CN Platinum, amminedichloro[2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-1H-imidazole-1-acetamide-N3]-, (SP-4-3)- (9CI) (CA INDEX NAME)



IT **152721-37-4**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(immunocytochem. labeling of aerobic and hypoxic mammalian cells using a platinated deriv. of EF5)

RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)

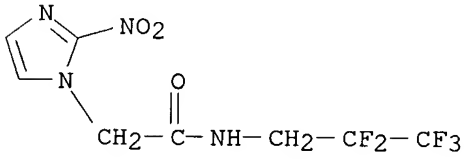


L11 ANSWER 25 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:589027 CAPLUS
DOCUMENT NUMBER: 129:260386
TITLE: An effective synthetic route to EF5
AUTHOR(S): Baird, Ian R.; Skov, Kirsten A.; James, Brian R.; Rettig, Steven J.; Koch, Cameron J.
CORPORATE SOURCE: Department of Chemistry, University of British Columbia, Vancouver, BC, V6T 1Z1, Can.
SOURCE: Synthetic Communications (1998), 28(19), 3701-3709
CODEN: SYNCAV; ISSN: 0039-7911
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB EF5 (a 2-nitroimidazole contg. an N-(pentafluoropropyl)acetamide substituent) is a very sensitive probe for quantifying the amt. of hypoxia within cells; a much improved, short step, synthetic procedure is described for EF5, whose X-ray structure is also presented.

IT **152721-37-4P**, EF5
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of (nitroimidazolyl)(pentafluoropropyl)acetamide)

RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)

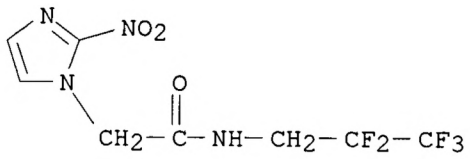


L11 ANSWER 36 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:293265 CAPLUS
DOCUMENT NUMBER: 125:4533
TITLE: Biodistribution of the nitroimidazole EF5 (2-[2-nitro-1H-imidazol-1-yl]-N-(2,2,3,3,3-pentafluoropropyl)acetamide) in mice bearing subcutaneous EMT6 tumors
AUTHOR(S): Laughlin, K. M.; Evans, S. M.; Jenkins, W. T.; Tracy, M.; Chan, C. Y.; Lord, E. M.; Koch, C. J.
CORPORATE SOURCE: Dep. Radn. Oncology, Univ. Pennsylvania, Philadelphia, PA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1996), 277(2), 1049-1057
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The characteristic redn. and binding of nitroimidazoles to cellular macromols. in the absence of oxygen allows their use for detection and characterization of hypoxia. The biodistribution of a new nitroimidazole, EF5 (2-[2-nitro-1H-imidazol-1-yl]-N-(2,2,3,3,3-pentafluoropropyl)acetamide), in mice bearing EMT6 tumors is described. Detection methods based on radioactivity and monoclonal antibody techniques are compared for liver and tumor. All nonexcretory tissues demonstrated similar levels of radioactivity at 0.5 h postinjection of drug, demonstrating equiv. access of EF5 to all tissues. At 24 h, when unbound drug has been cleared, the tissues with the highest binding are the liver, esophagus, bladder and tumor. Typically, liver tissue contains the highest level of radio-activity at this time. Examn. of tumor and liver tissue by use of fluorescence microscopy and Cy3-bound monoclonal antibodies specific for EF5 adducts showed the patterns of binding in tumor are considerably more heterogeneous than those of liver. Histograms of fluorescence intensity, with use of these antibodies, demonstrate av. and maximal binding higher in tumors than in the liver. This divergence from the radioactivity data was detd. to be unrelated to sampling error, differential antibody access or staining efficiency of liver vs. tumor tissue. A possible cause is the scavenging of radioactive drug metabolites by liver. The data presented herein suggest that EF5 is useful as a hypoxia detector and that monoclonal antibody detection methods can give detailed information on the distribution of EF5 binding. This technol. may allow an accurate estn. of the oxygenation and/or nitroreductase levels in both tumor and normal tissues.

IT **152721-37-4**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(biodistribution of nitroimidazole EF5 in tumor and liver and other tissues in relation to hypoxia detection)

RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)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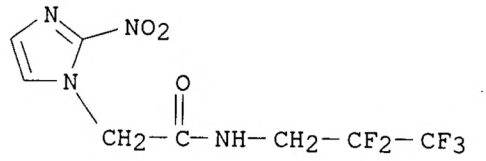
CH2 C NH CH2 CF2 CF3

L11 ANSWER 37 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:60562 CAPLUS
DOCUMENT NUMBER: 124:139857
TITLE: 2-Nitroimidazole (EF5) binding predicts radiation resistance in individual 9L s.c. tumors
AUTHOR(S): Evans, Sydney M.; Jenkins, W. Timothy; Joiner, Barbara; Lord, Edith M.; Koch, Cameron J.
CORPORATE SOURCE: Sch. of Veterinary Medicine, Univ. of Pennsylvania, Pennsylvania, PA, 19104, USA
SOURCE: Cancer Research (1996), 56(2), 405-11
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The presence of hypoxic tumor cells cell is known to be an important cause of radiation treatment resistance in vivo. The ability to predict the presence and extent of hypoxic cells in individual tumors would allow the addn. of specific "antihypoxia"-based treatment regimes. Hypoxia can be monitored by measuring the binding of 2-nitroimidazoles. We have tested the hypothesis that binding of EF5, a fluorinated deriv. of the 2-nitroimidazole, Etanidazole, can predict radioresistance in individual tumors. Fischer rats bearing 9L s.c. tumors were given injections i.v. with EF5 3 h before irradn. and tumor harvest. Tumor cells were dissocd. for flow cytometric anal. and plating efficiency studies. EF5 binding was detected via monoclonal antibodies conjugated to the orange emitting dye, Cy3. In air breathing rats, for a given radiation dose, a large amt. of variation in plating efficiency was seen. However, there was minimal variability of the plating efficiency for tumors irradiated in euthanized animals (hypoxic tumors; correlation coeff. for the fitted curve = 0.93) and in cells dissocd. from tumors and irradiated in suspension (correlation coeff. for the fitted curve = 0.99), suggesting that varying sensitivity to the cell disaggregation technique was not responsible. In contrast, a good correlation between the relative radiation resistance or hypoxic survival and EF5 binding of "moderately" hypoxic cells in air breathing rats was identified using these techniques. In these 9L s.c. tumors, intertumor variation in oxygenation accounted for most of the range in individual tumor radiation response, and this was found to be independent of tumor size. This study provides evidence for the application of EF5 binding with monoclonal antibody detection as an in vivo predictive assay of individual tumor hypoxia and resultant therapy resistance.

IT **152721-37-4**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(2-nitroimidazole (EF5) binding to tumor hypoxic fractions predicts x-ray resistance in individual 9L s.c. tumors)

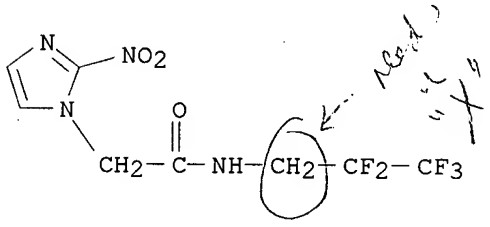
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)



L11 ANSWER 49 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:101090 CAPLUS
DOCUMENT NUMBER: 120:101090
TITLE: Detection of hypoxic cells by monoclonal antibody recognizing 2-nitroimidazole adducts
AUTHOR(S): Lord, Edith M.; Harwell, Lee; Koch, Cameron J.
CORPORATE SOURCE: Cancer Cent., Univ. Rochester, Rochester, NY, 14642, USA
SOURCE: Cancer Research (1993), 53(23), 5721-6
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A pentafluorinated deriv. [EF5; 2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide] of etanidazole was synthesized with the expectation of lessening some of the non-oxygen-dependent variability in adduct formation obsd. previously with other nitroarom. compds. EF5-protein conjugates, prepd. by radiochem. redn., were found to be immunogenic and allowed the development of monoclonal antibodies. One of these antibodies, ELK2-4, has been characterized and found to be highly specific for the EF5 adducts whether produced radiochem. or by cellular bioreductive metab. The 9L rat glioma cells pretreated with EF5 under hypoxic, compared with aerobic, conditions were readily discriminated immunochem. using fluorochrome-conjugated secondary antibodies which recognize the ELK2-4 antibody subtype (IgG1). Similarly, the central region of multicellular spheroids, composed of EMT6 mouse mammary sarcoma cells, was selectively visualized by immunohistochem. after the spheroids were incubated for 4 h in 0.5 mM EF5. Tumor biopsy, prepn., and immunohistochem. staining 24 h after treatment of tumor-bearing animals with drug also demonstrated high contrast regions within EMT6 mouse or Morris 7777 hepatoma rat tumors. The use of this new compd. and its highly specific monoclonal antibody may allow elucidation of bioreductive metab. of the nitroheterocyclics and significantly improve technologies for the quantitation of tissue pO2.

IT **152721-37-4**
RL: ANST (Analytical study)
(in hypoxic cell detection with monoclonal antibodies)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)

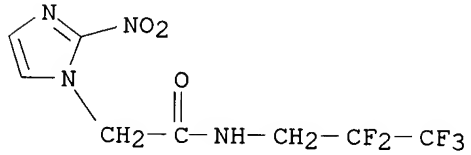


L11 ANSWER 39 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:936067 CAPLUS
DOCUMENT NUMBER: 124:44585
TITLE: Identification of hypoxia in cells and tissues of epigastric 9L rat glioma using EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide]
AUTHOR(S): Evans, S M.; Joiner, B.; Jenkins, W T.; Laughlin, K M.; Lord, E M.; Koch, C J.
CORPORATE SOURCE: Schools Veterinary Medicine (Clinical Studies), University Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: British Journal of Cancer (1995), 72(4), 875-82
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Macmillan Scientific & Medical Division
DOCUMENT TYPE: Journal
LANGUAGE: English

AB One of the most sensitive hypoxia detection methods is based on the observation that binding of nitroimidazoles to cellular macromols. occurs as a result of hypoxia-dependent bioredn. by cellular nitroreductases. Nitroimidazole-binding techniques provide measurements of hypoxia to virtually and degree of spatial resoln. and with a multiplicity of techniques. This paper demonstrates hypoxia imaging using in vivo EF5 binding with detection by a fluorochrome-conjugated monoclonal antibody. The authors investigated these techniques in the 9L glioma tumor, in part because the exact nature of the hypoxia in this tumor system is controversial. The results demonstrate that following i.v. injection of EF5, binding and detection using a monoclonal antibody in 9L gliomas is specific and oxygen dependent. Detection of binding using fluorescence microscopy can be performed on frozen tissues; tissue sections can be counterstained with haematoxylin and eosine for light microscopic anal. Alternatively, the distribution of hypoxia in a tumor can be inferred by examg. individual tumor cells using flow cytometric techniques. Based upon the results presented herein, the radiation-resistant phenotype of 9L epigastric tumors grown in the labs. can be assocd. with the presence of hypoxic cells.

IT **152721-37-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(identification of hypoxia in cells and tissues of epigastric 9L rat glioma using EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide])

RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)

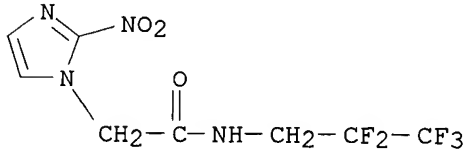


L11 ANSWER 38 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:1002637 CAPLUS
DOCUMENT NUMBER: 124:52283
TITLE: Mapping of the vascular endothelial growth factor-producing hypoxic cells in multicellular tumor spheroids using a hypoxia-specific marker
AUTHOR(S): Waleh, Nahid S.; Brody, Michael D.; Knapp, Merrill A.; Mendonca, Holly L.; Lord, Edith M.; Koch, Cameron J.; Laderoute, Keith R.; Sutherland, Robert M.
CORPORATE SOURCE: Cellular and Mol. Biol. Lab., Life Sci. DIv., Menlo Park, CA, 94025, USA
SOURCE: Cancer Research (1995), 55(24), 6222-6
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have investigated the hypoxia inducibility of vascular endothelial growth factor (VEGF) in multicellular tumor spheroids of HT29 cells using a monoclonal antibody to a fluorinated bioreductive drug, EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide], a chem. probe for hypoxia. The authors have shown that VEGF expression is predominantly localized in interior spheroid cells that are sufficiently hypoxic to bioreductively activate the 2-nitroimidazole and produce immunol. detectable adducts of the EF5 compd. Northern blotting analyses demonstrated that VEGF165 is the predominant form of VEGF produced by HT29 cells and that the phorbol ester 12-O-tetradecanoylphorbol-13-acetate did not induce VEGF expression. This study demonstrates that VEGF expression is up-regulated in response to hypoxia and in the microenvironments found in human multicellular tumor spheroids. This investigation also illustrates the utility of the EF5 binding in multicellular tumor spheroids as a means of studying the expression and regulation of hypoxia-inducible genes.

IT **152721-37-4**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(vascular endothelial growth factor expression colocalization with EF5 binding in hypoxic regions of multicellular tumor spheroids of human HT29 cells)

RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)

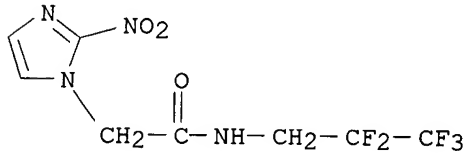


L11 ANSWER 40 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:936066 CAPLUS
DOCUMENT NUMBER: 124:44665
TITLE: Oxygen dependence of cellular uptake of EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide]: Analysis of drug adducts by fluorescent antibodies vs. bound radioactivity
AUTHOR(S): Koch, C. J.; Evans, S. M.; Lord, E. M.
CORPORATE SOURCE: Radiation Oncology, University Pennsylvania, Philadelphia, PA, 19104-6072, USA
SOURCE: British Journal of Cancer (1995), 72(4), 869-74
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Macmillan Scientific & Medical Division
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present studies were initiated to quantitate the oxygen dependence of bioreductive metab.-induced binding of EF5, a pentafluorinated deriv. of the 2-nitroimidazole, etanidazole. Two different assays were compared: first, radioactive drug incorporation into cell lysates, which provides a direct measure of drug metab. or uptake; second, monoclonal antibody detection of cellular macromol. adducts of EF5 after whole cell permeabilization and fixing. The antibodies (a single clone designated ELK3-5I) were conjugated with the fluorescent dye Cy3, with fluorescence detd. by fluorescence microscopy and flow cytometry. For the two cell lines tested (V79 Chinese hamster fibroblasts and 9L rat glioma), the oxygen dependence of binding was the same for the two techniques. Using the antibody binding technique, the fluorescence signal was highly reproducible between expts., resistant to light or chem. bleaching and stable over time following cell or tissue staining. Flow cytometric anal. of cells from rat 9L tumors treated with EF5 in vivo or in vitro showed a distribution of fluorescent signal which was very compatible, on both a relative and abs. basis, with the in vitro results. The results indicate that immunofluorescent techniques provide a quant. assay for bioreductive drug adducts, and therefore may be able to measure the abs. oxygen concn. distribution in cell populations and tissues of interest.

IT **152721-37-4**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(oxygen dependence of cellular uptake of EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide]: anal. of drug adducts by fluorescent antibodies vs. bound radioactivity)

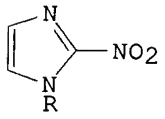
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)



L11 ANSWER 51 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:6504 CAPLUS
DOCUMENT NUMBER: 114:6504
TITLE: Preparation of 3-(2-nitroimidazolo)-2,2-difluoropropionamides and analogs as radiosensitizers
INVENTOR(S): Kagiya, Tsutomu; Abe, Mitsuyuki; Nishimoto, Seiichi; Shibamoto, Yuta; Otomo, Susumu; Tanami, Tohru; Shimokawa, Kazuhiro; Yoshizawa, Toru; Hisanaga, Yorisato
PATENT ASSIGNEE(S): Nishijima, Yasunori, Japan; Taisho Pharmaceutical Co., Ltd.; Daikin Industries, Ltd.
SOURCE: Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 373630	A1	19900620	EP 1989-123062	19891213
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 2005261	AA	19900614	CA 1989-2005261	19891212
US 4977273	A	19901211	US 1989-448909	19891212
AU 8946713	A1	19900621	AU 1989-46713	19891213
AU 625581	B2	19920716		
ZA 8909503	A	19900926	ZA 1989-9503	19891213
JP 02275863	A2	19901109	JP 1989-325437	19891214

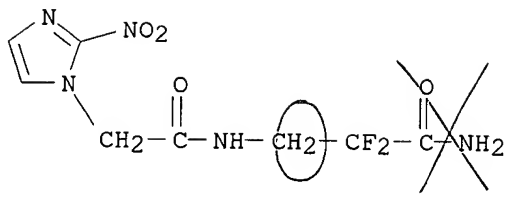
PRIORITY APPLN. INFO.: JP 1988-315974 19881214
OTHER SOURCE(S): CASREACT 114:6504; MARPAT 114:6504
GI



I

AB The title compds. [I; R = CH2CFXCH2OR1; R1 = CH2CH(OR2)CH2OR2, (CH2)lOR2, (CH2)lCOR2, (CH2)m(CF2)n[CONH(CHR3)r(CF2)p]qZ, etc.; R2 = H, OH (sic), alkyl, acyl; R22 = PhCH, Me2C; R3 = H, alkyl; X = H, halo; Z = H, CO2R3, CO2H, CONH2, etc.; l = 1-3; m, n = 0-4; p = 0-2; q, r = 0-3] were prepd. as hypoxic cell sensitizers. Thus, I (R = CH2CF2CO2Me) was stirred 1 h with H2NCH2CH2CO2Me.HCl in MeOH contg. KOH and the product stirred 2 days with aq. NH3-MeOH contg. KOH to give I (R = CH2CF2CONHCH2CH2CONH2) which gave cell-survival rate of EMT-6 tumor cells X-irradiated in mouse thigh 66% that of unirradiated cells after administration of 100 mg/kg i.p.

IT **130777-35-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as radiosensitizer)
RN 130777-35-4 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-amino-2,2-difluoro-3-oxopropyl)-2-nitro- (9CI) (CA INDEX NAME)



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NEWS 2	Apr 08	"Ask CAS" for self-help around the clock
NEWS 3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4	Apr 09	ZDB will be removed from STN
NEWS 5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 9	Jun 03	New e-mail delivery for search results now available
NEWS 10	Jun 10	MEDLINE Reload
NEWS 11	Jun 10	PCTFULL has been reloaded
NEWS 12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS 14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS 15	Jul 30	NETFIRST to be removed from STN
NEWS 16	Aug 08	CANCERLIT reload
NEWS 17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18	Aug 08	NTIS has been reloaded and enhanced
NEWS 19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 23	Sep 03	JAPIO has been reloaded and enhanced
NEWS 24	Sep 16	Experimental properties added to the REGISTRY file
NEWS 25	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 26	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 27	Oct 21	EVENTLINE has been reloaded
NEWS 28	Oct 24	BEILSTEIN adds new search fields
NEWS 29	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 30	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS 31	Nov 18	DKILIT has been renamed APOLLIT
NEWS 32	Nov 25	More calculated properties added to REGISTRY
NEWS 33	Dec 02	TIBKAT will be removed from STN
NEWS 34	Dec 04	CSA files on STN
NEWS 35	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 36	Dec 17	TOXCENTER enhanced with additional content
NEWS 37	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 38	Dec 30	ISMEC no longer available

NEWS 39 Jan 13 Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 40 Jan 21 NUTRACEUT offering one free connect hour in February 2003
NEWS 41 Jan 21 PHARMAML offering one free connect hour in February 2003
NEWS 42 Jan 29 Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC

NEWS EXPRESS January 6 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
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STRUCTURE FILE UPDATES: 11 FEB 2003 HIGHEST RN 488780-79-6
DICTIONARY FILE UPDATES: 11 FEB 2003 HIGHEST RN 488780-79-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

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http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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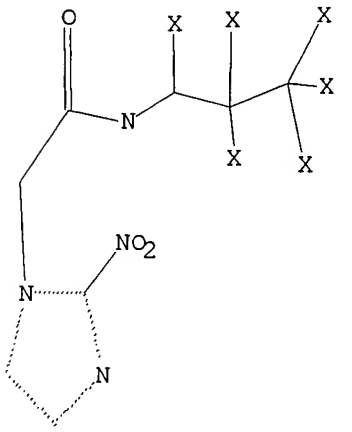
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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FULL SEARCH INITIATED 16:06:54 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 13 TO ITERATE

100.0% PROCESSED 13 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

L2 0 SEA SSS FUL L1

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L3 STRUCTURE UPLOADED

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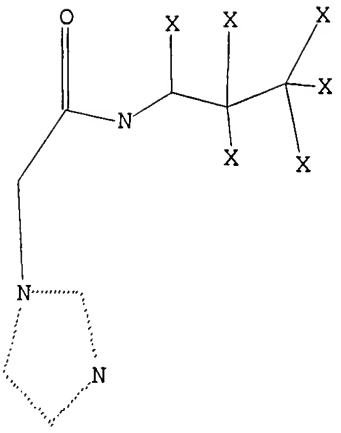
L3 HAS NO ANSWERS
L3 STR



Structure attributes must be viewed using STN Express query preparation.

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100.0% PROCESSED       3 ITERATIONS                                 0 ANSWERS
SEARCH TIME: 00.00.02

L4             0 SEA SSS FUL L3

=>
Uploading 10049284.str

L5       STRUCTURE UPLOADED

=> d
L5 HAS NO ANSWERS
L5                STR
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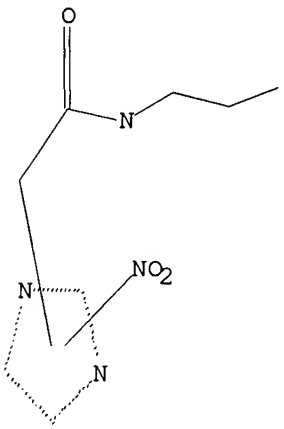

Structure attributes must be viewed using STN Express query preparation.

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100.0% PROCESSED    6926 ITERATIONS                          91 ANSWERS
SEARCH TIME: 00.00.01

L6            91 SEA SSS FUL L5

=> s l6 and caplus/lc
      26154954 CAPLUS/LC
L7           88 L6 AND CAPLUS/LC

=> s l6 not l7
L8            3 L6 NOT L7

=> d 1-3
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L8 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 405279-27-8 REGISTRY
CN 1H-Imidazole-1-acetamide, N-(3-hydroxypropyl)-2-methyl-4-nitro- (9CI) (CA INDEX NAME)
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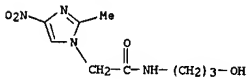
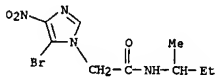
MF C9 H14 N4 O4
SR Chemical Library
LC STN Files: CHEMCATS



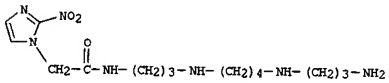
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L8 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 362596-32-5 REGISTRY
CN 1H-Imidazole-1-acetamide, 5-bromo-N-(1-methylpropyl)-4-nitro- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C9 H13 Br N4 O3
SR Chemical Library
LC STN Files: CHEMCATS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L8 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2003 ACS
RN 165062-81-7 REGISTRY
CN 1H-Imidazole-1-acetamide, N-[3-[[4-[(3-aminopropyl)amino]butyl]amino]propyl]-2-nitro- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C15 H29 N7 O3
CI COM
SR CA



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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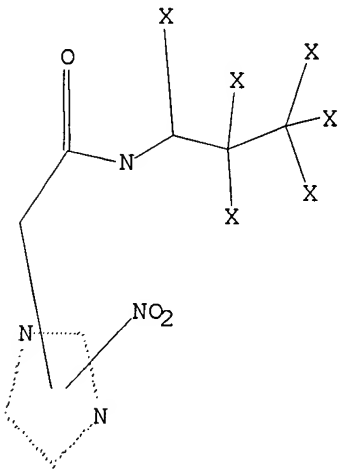
L9 STRUCTURE UPLOADED

=> d
L9 HAS NO ANSWERS
L9 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l9 ful
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FULL SCREEN SEARCH COMPLETED - 11 TO ITERATE

100.0% PROCESSED 11 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

L10 0 SEA SSS FUL L9

=> fil caplus
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	602.66	602.87

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FILE LAST UPDATED: 11 Feb 2003 (20030211/ED)

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FILE 'REGISTRY' ENTERED AT 16:06:38 ON 12 FEB 2003
L1 STRUCTURE UPLOADED
L2 0 S L1 FUL
L3 STRUCTURE UPLOADED
L4 0 S L3 FUL
L5 STRUCTURE UPLOADED
L6 91 S L5 FUL
L7 88 S L6 AND CAPLUS/LC
L8 3 S L6 NOT L7
L9 STRUCTURE UPLOADED
L10 0 S L9 FUL

FILE 'CAPLUS' ENTERED AT 16:10:17 ON 12 FEB 2003

=> s l6
L11 62 L6

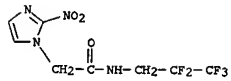
=> d 1-62 ibib abs hitstr

L11 ANSWER 1 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:526269 CAPLUS
DOCUMENT NUMBER: 137:292513
TITLE: Effects of hyperglycemia on oxygenation, radiosensitivity and bioenergetic status of subcutaneous RIF-1 tumors
AUTHOR(S): Nadal-Desbarats, L.; Poptani, H.; Oprysko, P.; Jenkins, W. T.; Busch, T. M.; Nelson, D. S.; Glickson, J. D.; Koch, C. J.; Evans, S. M.
CORPORATE SOURCE: Department of Radiology, University of Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: International Journal of Oncology (2002), 21(1), 103-110
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Since tissue O tension is a balance between delivery and consumption of O, considerable effort was directed at increasing the former and/or decreasing the latter. Techniques to decrease the rate of cellular O consumption (increasing the distance O can diffuse into tissues) include increasing glycolysis by administering supraphysiol. levels of glucose. We have examd. the effect of hyperglycemia produced by i.v. glucose infusion on the tissue oxygenation and radiation response of s.c. implanted murine radiation induced fibrosarcomas (RIF-1). A 0.3 M glucose soln. was delivered via tail vein injection according to a protocol that maintained glucose at a plasma concn. of 17.+-.1 mM. The effect of this treatment on radiation response (clonogenic and growth delay studies), tumor oxygenation (needle electrode pO2 and 2-[2-nitro-1H-imidazol-1-yl]-N-(2,2,3,3,3-pentafluoropropyl) acetamide (EF5) binding), and tumor bioenergetics and pH (31P NMR spectroscopy) was examd. Systemic measurements included hematocrit and blood glucose and lactate concns. The results of these studies suggest that these s.c. implanted RIF-1 tumors are both radiobiol. and metabolically hypoxic and that i.v. glucose infusion is not an effective method of modifying this metabolic state.

IT **152721-37-4**, EF5
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(hyperglycemia effect on oxygenation, radiosensitivity, and EF5 binding in s.c. RIF-1 tumors)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
(CA INDEX NAME)

L11 ANSWER 1 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

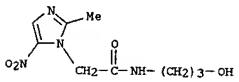


REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:446905 CAPLUS
DOCUMENT NUMBER: 138:66150
TITLE: Modeling of the anticancer action for radical derivatives of nitroazoles: quantitative structure-activity relationship (QSAR) study
AUTHOR(S): Khlebnikov, Andrei; Schepetkin, Igor; Se Kwon, Byoung
CORPORATE SOURCE: Altai State Technical University, Barnaul, Russia
SOURCE: Cancer Biotherapy & Radiopharmaceuticals (2002), 17(2), 193-203
CODEN: CBRAFJ; ISSN: 1084-9785
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

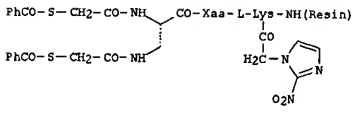
AB A QSAR anal. of the anti-tumor, anti-metastasis and anti-colony formation (for metastatic colonies) activities of eighteen nitroazoles (including metronidazole and hypoxic radiosensitizers RP-170, KU-2285 and sanazole (drug AK-2123)) and their nitro and nitroso anion radical derivs. against melanoma B16 in mice has been performed. The QSAR models were built with the use of the frontal polygon method. This approach has features of different 3D QSAR methodologies and belongs to the group of "indirect" methods. The procedure allows to build robust models with high predictive ability even in series of diverse and conformationally flexible compds. Key at. characteristics accompany the geometrical requirements in the anal. of local 3D mol. similarity. By variation of wt. coeffs. for hydrophobicity, refraction increments, and partial charge it is possible to achieve better quality of QSAR and evaluate the importance of each characteristic for biol. activity under consideration. It was found that hydrophobicity, molar refraction and charge characteristics of nitro anion radical derivs. are more significant for interaction with mol. targets than those of the parent compds. and of the nitroso anion radical derivs. Size and hydrophobic properties of substituents in nitro anion radicals play significant role for ligand-target interaction in the processes of inhibition of metastatic spreading and growth of metastatic colonies by nitroazoles. A scheme of competitive interaction of parent nitroazoles and their anion radicals with a target in organism is suggested. It can be concluded that the step of one-electron redn. of nitroazoles can be

L11 ANSWER 2 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
important for anticancer activity of these drugs.
IT **205811-49-0**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modeling of anticancer action for radical derivs. of nitroazoles and their quant. structure-activity relationship (QSAR))
RN 205811-49-0 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-hydroxypropyl)-2-methyl-5-nitro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:169416 CAPLUS
DOCUMENT NUMBER: 136:355472
TITLE: A Simple Two-Step Approach for Introducing a Protected Diaminedithiol Chelator during Solid-Phase Assembly of Peptides
AUTHOR(S): Gariepy, Jean; Remy, Sandrine; Zhang, Xiuguo; Ballinger, James R.; Bolewska-Pedyczak, Eleonora; Rauth, Michael; Bisland, Stuart K.
CORPORATE SOURCE: Department of Medical Biophysics, Division of Molecular and Structural Biology, University of Toronto, Ontario Cancer Institute, Princess Margaret Hospital, Toronto, ON, M5G 2M9, Can.
SOURCE: Bioconjugate Chemistry (2002), 13(3), 679-684
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

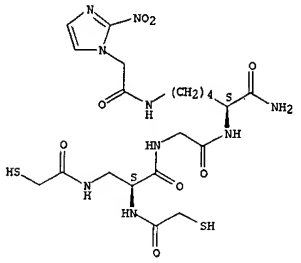


I

AB A simple synthetic strategy is described to incorporate a protected diaminedithiol (N2S2) chelator during Fmoc-based, solid-phase synthesis of short peptides, such that these peptides could, then, be efficiently labeled with technetium-99m (99mTc). The chelator was assembled at the N-terminus of peptides in a two-step procedure where the deprotected terminal amino group was first reacted with di-Fmoc-L-diaminopropionic acid. The two protected amino groups were then simultaneously deprotected and subsequently reacted with S-benzoylthiolglycolic acid to generate a protected N2S2 chelator. Each peptide construct was composed of a C-terminal lysine residue and an N-terminal diaminopropionic moiety modified to create the chelator site. The Lys .epsilon.-amino group was further derivatized with a nitroimidazole group to facilitate cellular retention. For example, resin-bound peptides I (Xaa = Gly, L-Asp, L-Lys, L-Asn, L-Ala, nil) were prepd. I was then cleaved from the resin support,

L11 ANSWER 3 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
purified, and labeled with [99mTc]pertechnetate. Optimal labeling yields of >70% were achieved around neutral pH and heating at 75.degree. for 10 min. Purified 99mTc-labeled constructs were found to accumulate in Chinese hamster ovary (CHO) cells in vitro as a function of charge and hydrophobicity.
IT **422309-59-9DP**, 99technetium complexes **422309-61-3DP**, 99technetium complexes **422309-62-4DP**, 99technetium complexes **422309-63-5DP**, 99technetium complexes **422309-64-6DP**, 99technetium complexes **422309-65-7DP**, 99technetium complexes
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of and in vitro cellular uptake of 99Tc-labeled peptides with diaminedithiol chelators)
RN 422309-59-9 CAPLUS
CN L-Lysinamide, N-(mercaptoacetyl)amino]-L-alanylglycyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

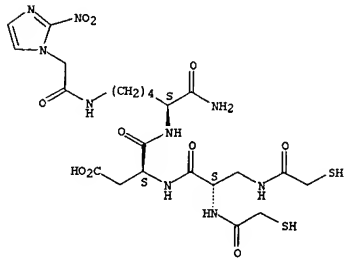
Absolute stereochemistry.



RN 422309-61-3 CAPLUS
CN L-Lysinamide, N-(mercaptoacetyl)-3-[(mercaptoacetyl)amino]-L-alanyl-L-.alpha.-aspartyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

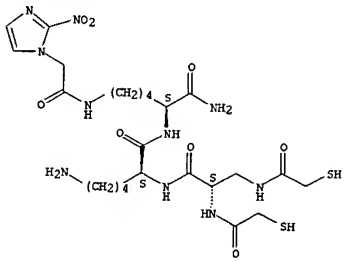
Absolute stereochemistry.

L11 ANSWER 3 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 422309-62-4 CAPLUS
CN L-Lysinamide, N-(mercaptoacetyl)-3-[(mercaptoacetyl)amino]-L-alanyl-L-lysyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

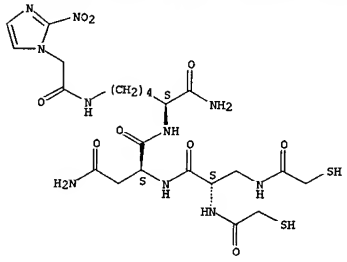
Absolute stereochemistry.



RN 422309-63-5 CAPLUS
CN L-Lysinamide, N-(mercaptoacetyl)-3-[(mercaptoacetyl)amino]-L-alanyl-L-asparaginyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

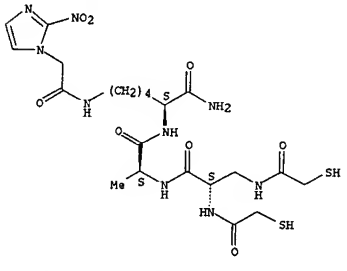
Absolute stereochemistry.

L11 ANSWER 3 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 422309-64-6 CAPLUS
CN L-Lysinamide, N-(mercaptoacetyl)-3-[(mercaptoacetyl)amino]-L-alanyl-L-alanyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

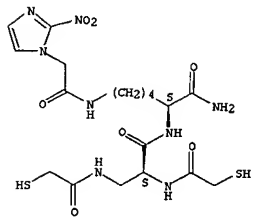
Absolute stereochemistry.



RN 422309-65-7 CAPLUS
CN L-Lysinamide, N-(mercaptoacetyl)-3-[(mercaptoacetyl)amino]-L-alanyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L11 ANSWER 3 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

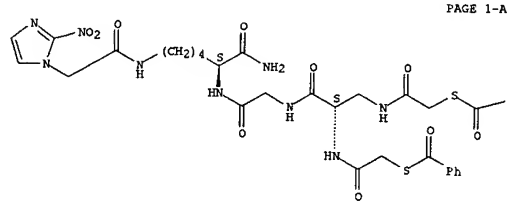


IT **422309-53-3P 422309-54-4P 422309-55-5P**
422309-56-6P 422309-57-7P 422309-58-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(solid-phase prepn. of peptides contg. a protected diaminedithiol chelator for 99Tc)

RN 422309-53-3 CAPLUS
CN L-Lysinamide,
N-[(benzoylthio)acetyl]-3-[[(benzoylthio)acetyl]amino]-L-alanylglycyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

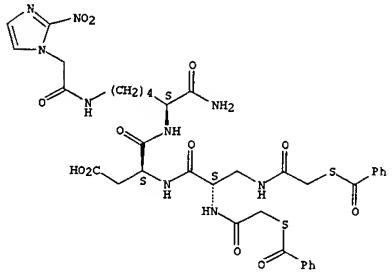
Absolute stereochemistry.

PAGE 1-A



L11 ANSWER 3 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

PAGE 1-B



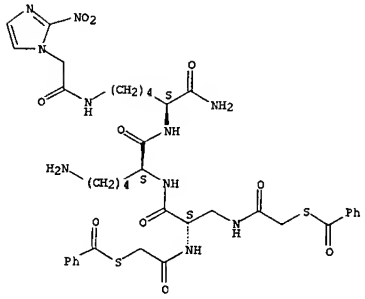
RN 422309-54-4 CAPLUS
CN L-Lysinamide,
N-[(benzoylthio)acetyl]-3-[[(benzoylthio)acetyl]amino]-L-alanyl-L-.alpha.-asparty1-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 422309-55-5 CAPLUS
CN L-Lysinamide,
N-[(benzoylthio)acetyl]-3-[[(benzoylthio)acetyl]amino]-L-alanyl-L-lysyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

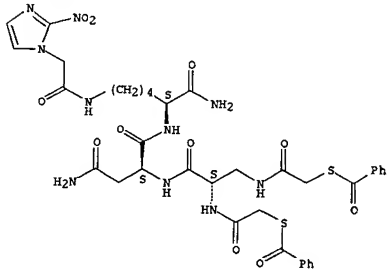
Absolute stereochemistry.

L11 ANSWER 3 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 422309-56-6 CAPLUS
CN L-Lysinamide,
N-[(benzoylthio)acetyl]-3-[[(benzoylthio)acetyl]amino]-L-alanyl-L-asparaginyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

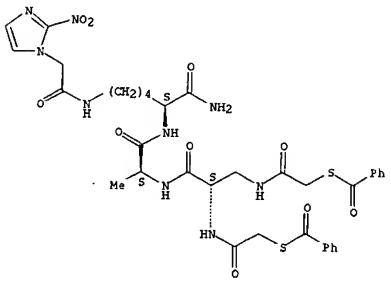


RN 422309-57-7 CAPLUS
CN L-Lysinamide,
N-[(benzoylthio)acetyl]-3-[[(benzoylthio)acetyl]amino]-L-

L11 ANSWER 3 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

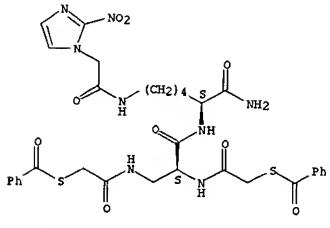
alanyl-L-alanyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 422309-58-8 CAPLUS
CN L-Lysinamide,
N-[(benzoylthio)acetyl]-3-[[(benzoylthio)acetyl]amino]-L-alanyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

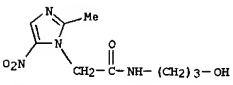


REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

L11 ANSWER 4 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:109891 CAPLUS
DOCUMENT NUMBER: 137:163307
TITLE: Quantitative structure-activity relationships (QSAR)
for antitumor activity of nitroazoles: A comparative
analysis for the parent compounds and their nitro anion radical and nitroso anion radical derivatives
AUTHOR(S): Khlebnikov, Andrei; Schepetkin, Igor; Kim, Byung Sam;
Kwon, Byoung Se
CORPORATE SOURCE: Altai State Technical University, Barnaul, 656099, Russia
SOURCE: Proceedings - KORUS 2001, the Korea-Russia International Symposium on Science and Technology, 5th, Tomsk, Russian Federation, June 26-July 3, 2001
(2001), Volume 3, 10-14. Institute of Electrical and
Electronics Engineers: New York, N. Y.
CODEN: 69CGH4; ISBN: 0-7803-7008-2
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A QSAR anal. of the antitumor, antimetastatic and anti-colony formation
(for metastatic colonies) activities of eighteen nitroazoles and their nitro anion radical and nitroso anion radical derivs. against melanoma B16
in mice is reported. The QSAR models were built with the use of the frontal polygon method. This approach has features of different 3D QSAR
methodologies. The procedure allows to build robust models with high predictive ability even in series of diverse and conformationally flexible
compds. Key at. characteristics (hydrophobicity and refraction increments, partial charge) accompany the geometrical requirements in the
anal. of local 3D mol. similarity. By variation of wt. coeffs. for these
properties it is possible to achieve better quality of QSAR and evaluate
the importance of each characteristic for biol. activity under consideration. It is the evidence that hydrophobicity, molar refraction
and charge characteristics of nitro anion radical derivs. are more significant for interaction with mol. targets than those of the parent compds. and of the nitroso anion radical derivs. Thus, the step of one-electron redn. of nitroazoles can be important for antitumor, anti-metastatic and anti-colony formation activity of these drugs.
IT **205811-49-0**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(QSAR for antitumor activity of nitroazoles and corresponding nitro-
and nitroso-anion radicals)

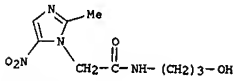
L11 ANSWER 4 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
RN 205811-49-0 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-hydroxypropyl)-2-methyl-5-nitro- (9CI) (CA
INDEX NAME)



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:109829 CAPLUS
DOCUMENT NUMBER: 137:179366
TITLE: Quantitative structure-activity relationships (QSAR)
for antitumor activity of nitroazoles: A comparative
analysis for the parent compounds and their nitro anion radical and nitroso anion radical derivatives
AUTHOR(S): Khlebnikov, Andrei; Schepetkin, Igor; Kim, Byung Sam;
Kwon, Byoung Se
CORPORATE SOURCE: Altai State Technical University, Barnaul, 656099, Russia
SOURCE: Proceedings - KORUS 2001, the Korea-Russia International Symposium on Science and Technology, 5th, Tomsk, Russian Federation, June 26-July 3, 2001
(2001), Volume 2, 58-62. Institute of Electrical and
Electronics Engineers: New York, N. Y.
CODEN: 69CGH4; ISBN: 0-7803-7008-2
DOCUMENT TYPE: Conference
LANGUAGE: English
AB QSAR anal. of the antitumor, antimetastatic and anti-colony formation (for
metastatic colonies) activities of eighteen nitroazoles and their nitro
anion radical and nitroso anion radical derivs. against melanoma B16 in
mice is reported. The QSAR models were built with the use of the frontal
polygon method. This approach has features of different 3D QSAR
methodologies. The procedure allows to build robust models with high predictive ability even in series of diverse and conformationally flexible
compds. Key at. characteristics (hydrophobicity and refraction increments, partial charge) accompany the geometrical requirements in the
anal. of local 3D mol. similarity. It was found that characteristics of
nitro anion radical derivs. are more significant for interaction with mol.
targets than those of the parent compds. and of the nitroso anion radical
derivs. Thus, the step of one-electron redn. of nitroazoles can be important for antitumor, antimetastatic and anti-colony formation activity
of these drugs.
IT **205811-49-0**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(quant. structure-activity relationships (QSAR) for antitumor activity
of nitroazoles and a comparative anal. for parent compds. and nitro anion radical and nitroso anion radical derivs.)

L11 ANSWER 5 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
RN 205811-49-0 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-hydroxypropyl)-2-methyl-5-nitro- (9CI) (CA
INDEX NAME)



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS
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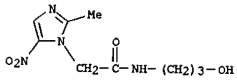
RECORD. ALL CITATIONS AVAILABLE IN THE RE

L11 ANSWER 6 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:54934 CAPLUS
DOCUMENT NUMBER: 136:288539
TITLE: Quantitative structure-activity relationships for nitroazoles with antitumor activity
AUTHOR(S): Khlebnikov, A. I.; Shchepetkin, I. A.; Akhmedzhanov, R. R.
CORPORATE SOURCE: Altai State Technical University, Barnaul, Russia
SOURCE: Pharmaceutical Chemistry Journal (Translation of Khimiko-Farmatsevticheskii Zhurnal) (2001), 35(6), 315-320
CODEN: PCJOAU; ISSN: 0091-150X
PUBLISHER: Kluwer Academic/Consultants Bureau
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The frontal polyhedra method was used to analyze the quant. structure-activity relation (QSAR) of nitroazoles with known antitumor, antimetastatic, and colony-inhibiting properties that were previously established within the framework of the exptl. model of melanoma B-16. The roles of various factors involved in the mol. recognition and the extent of participation of various structural fragments of mols. in the manifestation of these types of activity were studied. QSAR models were constructed for each of the biol. types studied. The base QSAR equations obtained for the no. of min. assignments in the optimum superimpositions (N0) and optimum boundary criterion (K0) values selected 3 and 0.10, resp., were optimized by sequential twofold redn. in the weighing coeffs. The difference in contributions of substituents, primarily of the azole heterocycle and nitro group, to the biol. activity manifestations for nitroazoles probably indicates the existence of different mol. targets (receptors) involved in the antitumor, antimetastatic, and colony-inhibiting interactions. The role of such targets can be played by enzymes possessing nitroreductase activity, by various surface and intracellular receptors.
IT **205811-49-0**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(QSAR of nitroazoles with antitumor activity)
RN 205811-49-0 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-hydroxypropyl)-2-methyl-5-nitro- (9CI) (CA
INDEX NAME)

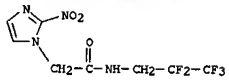
L11 ANSWER 6 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS
FORMAT
RECORD. ALL CITATIONS AVAILABLE IN THE RE

L11 ANSWER 7 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:790212 CAPLUS
DOCUMENT NUMBER: 136:67942
TITLE: Hypoxia-inducible factor-1.alpha. is an intrinsic marker for hypoxia in cervical cancer xenografts
AUTHOR(S): Vukovic, Vojislav; Haugland, Hans Kristian; Nicklee, Trudey; Morrison, Andrew J.; Hedley, David W.
CORPORATE SOURCE: Departments of Medical Biophysics, Ontario Cancer Institute/Princess Margaret Hospital, Toronto, ON, M5G 2M9, Can.
SOURCE: Cancer Research (2001), 61(20), 7394-7398
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The hypoxia-inducible factor 1 (HIF-1) is known to induce the expression of several proteins linked to the maintenance of oxygen homeostasis, cellular energy metab., and tumor progression. Its .alpha. subunit (HIF-1.alpha.) is stabilized under hypoxic conditions and, therefore, might represent an intrinsic marker for tissue, hypoxia. Here we report on the spatial relationship between HIF-1.alpha. and the nitroimidazole hypoxia marker EF5 in cervical carcinoma xenografts, and on their spatial relationship to tumor blood vessels. EF5 was administered to mice bearing ME180 and SiHa cervical cancer xenografts. Frozen tumor tissue sections, triple-stained for HIF-1.alpha., the endothelial cell marker CD31, and EF5, were imaged using wide-field multiparameter immunofluorescence microscopy. Expression levels of EF5 and HIF-1.alpha. were similar in ME180 xenografts, but the percentage of tumor area stained with EF5 was significantly smaller than the percentage of HIF-1.alpha.-pos. area in SiHa tumors. In both tumor types the EF5-HIF-1.alpha. overlap was statistically significant, thus confirming their spatial and temporal colocalization. Spatial distribution anal. of EF5 and HIF-1.alpha. is consistent with different pO2 value "thresholds" for EF5 binding and HIF-1.alpha. expression. Summarized, our results indicate that HIF-1.alpha. is a useful intrinsic marker for hypoxia in cervical carcinoma xenografts.
IT **152721-37-4**
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(hypoxia-inducible factor-1.alpha. as intrinsic marker for hypoxia in cervical carcinoma xenografts)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
(CA INDEX NAME)

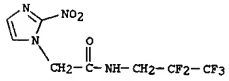
L11 ANSWER 7 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 8 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:644457 CAPLUS
DOCUMENT NUMBER: 137:29877
TITLE: Pharmacokinetics of EF5 [2-(2-nitro-1-H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide] in human patients: implications for hypoxia measurements in vivo by 2-nitroimidazoles
AUTHOR(S): Koch, C. J.; Hahn, S. M.; Rockwell, K., Jr.; Covey, J. M.; McKenna, W. G.; Evans, S. M.
CORPORATE SOURCE: University of Pennsylvania School of Medicine, Radiation Oncology, Philadelphia, PA, 19104-6072, USA
SOURCE: Cancer Chemotherapy and Pharmacology (2001), 48(3), 177-187
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objectives: Pharmacokinetic studies were performed on the 1st 28 patients enrolled in a phase I trial to det. the ability of EF5 [2-(2-nitro-1-H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide] to detect hypoxia in human tumors in the absence of patient toxicity. Methods: EF5 was made in purified form and formulated for i.v. injection by the National Cancer Institute. After obtaining consent from the patients, EF5 was administered and blood samples were drawn at various times over approx. 48 h. For most patients it was possible to collect total urine at approx. 8-h intervals. EF5 in plasma and urine was analyzed by high-performance liq. chromatog. Results: EF5's blood plasma concn. followed a simple exponential decay following infusion. The plasma half-life was 11.7 h and was not affected by drug dose (9 to 28 mg/kg), fractional urine recovery, patient wt., or gender. Abs. plasma values suggested even biodistribution of the drug throughout the soft tissue with a vol. of distribution equal to 0.56 l/kg. Despite the relatively high lipid partition coeff. (logP=0.6), EF5 was excreted primarily (.ltoreq. 70%) via kidney clearance. No drug metabolites (e.g. retaining the 2-nitroimidazole chromophore) were detected in either plasma or urine. No toxicity was found at drug doses adequate to detect tumor hypoxia. Conclusions: Currently held paradigms of 2-nitroimidazole metab. (e.g. clearance rate and toxicity as affected by octanol/water partition coeff.) are discussed. The results reported herein suggest that EF5 is biol. stable with predictable pharmacokinetics. EF5's consistent half-life and

L11 ANSWER 8 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
clearance properties will allow quant. anal. of EF5 binding relative to tissue oxygen levels.
IT **152721-37-4**, EF5
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetics of EF5 in human cancer patients)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
(CA INDEX NAME)



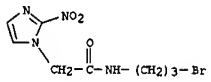
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 9 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:468223 CAPLUS
DOCUMENT NUMBER: 135:58183
TITLE: Nitroaromatic compounds for the detection of hypoxia
INVENTOR(S): Koch, Cameron J.; Kachur, Alexander V.; Evans, Sydney M.; Shiue, Chyng-yann; Baird, Ian R.; Skov, Kirsten A.; Dolbier, Jr William R.; Li, An-rong; James, Brian R.
PATENT ASSIGNEE(S): Trustees of the University of Pennsylvania, USA
SOURCE: U.S., 17 pp., Cont.-in-part of U.S. 5,843,404.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

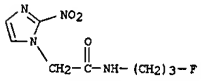
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6252087	B1	20010626	US 1998-123300	19980728
US 5540908	A	19960730	US 1994-286065	19940804
US 5843404	A	19981201	US 1996-598752	19960208

PRIORITY APPLN. INFO.: US 1992-978918 B2 19921119
US 1994-286065 A3 19940804
US 1996-598752 A2 19960208
OTHER SOURCE(S): MARPAT 135:58183
AB Nitroarom. compds. and immunogenic conjugates comprising a novel nitroarom. compd. and a carrier protein are disclosed. The invention further presents monoclonal antibodies highly specific for the claimed nitroarom. compds., the compds.' protein conjugates, the compds.' reductive byproducts, and adducts formed between the compds. and mammalian hypoxic cell tissue proteins. The invention is further directed to methods for detecting tissue hypoxia using immunohistol. techniques, non-invasive nuclear medicinal methods, or NMR. Diagnostic kits useful in practicing the methods of claimed invention are also provided.
IT **252736-27-9DP**, compds. contg. **252736-28-0P** **345658-88-0P** **345658-89-1P** **345658-90-4P** **345658-91-5P** **345658-92-6P** **345658-93-7P** **345658-94-8P**
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nitroarom. compds. for detection of hypoxia)
RN 252736-27-9 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-bromopropyl)-2-nitro- (9CI) (CA INDEX NAME)

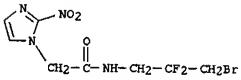
L11 ANSWER 9 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



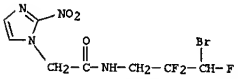
RN 252736-28-0 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-fluoropropyl)-2-nitro- (9CI) (CA INDEX
NAME)



RN 345658-88-0 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-bromo-2,2-difluoropropyl)-2-nitro- (9CI)
(CA INDEX NAME)

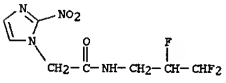


RN 345658-89-1 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-bromo-2,2,3-trifluoropropyl)-2-nitro- (9CI)
(CA INDEX NAME)

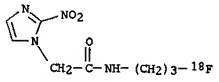


RN 345658-90-4 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2-bromo-3-fluoropropyl)-2-nitro- (9CI) (CA
INDEX NAME)

L11 ANSWER 9 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

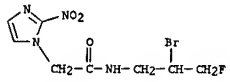


IT **252736-29-1P**
RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); THU
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nitroarom. compds. for detection of hypoxia)
RN 252736-29-1 CAPLUS
CN 1H-Imidazole-1-acetamide, N-[3-(fluoro-18F)propyl]-2-nitro- (9CI) (CA
INDEX NAME)

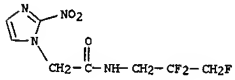


REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

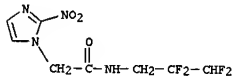
L11 ANSWER 9 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



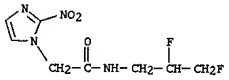
RN 345658-91-5 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3-trifluoropropyl)- (9CI) (CA
INDEX NAME)



RN 345658-92-6 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3-tetrafluoropropyl)- (9CI)
(CA INDEX NAME)

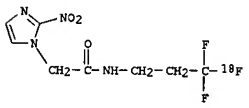


RN 345658-93-7 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2,3-difluoropropyl)-2-nitro- (9CI) (CA INDEX
NAME)



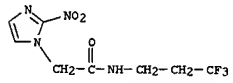
RN 345658-94-8 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,3,3-trifluoropropyl)- (9CI) (CA
INDEX NAME)

L11 ANSWER 10 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:322270 CAPLUS
DOCUMENT NUMBER: 135:76826
TITLE: Synthesis of [18F]-labeled EF3 [2-(2-nitroimidazol-1-yl)-N-(3,3,3-trifluoropropyl)acetamide], a marker for PET detection of hypoxia
AUTHOR(S): Josse, Olivier; Labar, Daniel; Georges, Benoit; Gregoire, Vincent; Marchand-Brynaert, Jacqueline
CORPORATE SOURCE: Unite de Chimie Organique et Medicinale, Universite catholique de Louvain, Louvain-la-Neuve, B-1348, Belg.
SOURCE: Bioorganic & Medicinal Chemistry (2001), 9(3), 665-675
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:76826
AB [18F]-2-(2-Nitroimidazol-1-yl)-N-(3,3,3-trifluoropropyl)acetamide ([18F]-EF3) has been prepd. in 65% chem. yield and 5% radiochem. yield by coupling 2,3,5,6-tetrafluorophenyl 2-(2-nitroimidazol-1-yl)acetate with [18F]-3,3,3-trifluoropropylamine. This original radiolabeled key synthon was obtained in 40% overall chem. yield by oxidative [18F]-fluorodesulfurization of Et N-phthalimido-3-aminopropanedithioate, followed by deprotection with hydrazine of the resulting [18F]-N-phthalimido-3,3,3-trifluoropropylamine. The process was performed within 90 min, from the [18F]-HF prodn. in the cyclotron to the purifn. of the final target.
IT **347190-26-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 347190-26-5 CAPLUS
CN 1H-Imidazole-1-acetamide, N-[3,3-difluoro-3-(fluoro-18F)propyl]-2-nitro- (9CI) (CA INDEX NAME)

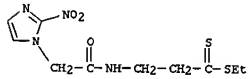


IT **180208-73-5P 347190-22-1P 347190-23-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of [18F]-labeled EF3 [2-(2-nitroimidazol-1-yl)-N-(3,3,3-

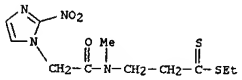
L11 ANSWER 10 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
trifluoropropyl)acetamide])
RN 180208-73-5 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoropropyl)- (9CI) (CA
INDEX NAME)



RN 347190-22-1 CAPLUS
CN Propane(dithioic) acid, 3-[[(2-nitro-1H-imidazol-1-yl)acetyl]amino]-, ethyl ester (9CI) (CA INDEX NAME)



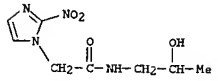
RN 347190-23-2 CAPLUS
CN Propane(dithioic) acid, 3-[methyl[(2-nitro-1H-imidazol-1-yl)acetyl]amino]-, ethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 11 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:162888 CAPLUS
DOCUMENT NUMBER: 134:363402
TITLE: New antimetastatic hypoxic cell radiosensitizers: design, synthesis, and biological activities of 2-nitroimidazole-acetamide, TX-1877, and its analogues
AUTHOR(S): Kasai, S.; Nagasawa, H.; Yamashita, M.; Masui, M.; Kuwasaka, H.; Oshodani, T.; Uto, Y.; Inomata, T.; Oka, S.; Inayama, S.; Hori, H.
CORPORATE SOURCE: Faculty of Engineering, Department of Biological Science and Technology, The University of Tokushima, Tokushima, 770-8506, Japan
SOURCE: Bioorganic & Medicinal Chemistry (2001), 9(2), 453-464
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We designed, based on the MO (MO) calcn., synthesized, and evaluated the biol. activities of the new antimetastatic hypoxic cell radiosensitizer, 2-nitroimidazole-acetamide, TX-1877, and its analogs. Each analog has an electron-affinic imidazole group, an acetamide group and a certain hydrophilic group to control its biol. effect, toxicity, and pharmacokinetics. In in vitro radiosensitization assay, most TX-1877 analogs, which have an electron affinity (EA) of more than 0.9 eV and partition coeff. (P) of more than 0.021, showed satisfactory enhancement ratios (ER > 1.60) at doses of 1 mM. On the other hand, imidazole analogs, such as TX-1908 (EA=0.67 eV), TX-1910 (EA=-0.34 eV) and TX-1931 (EA=-0.37 eV), which have low electron affinities, had an ER of 1.31 or less. TX-1877 and KIN-806 effectively inhibited tumor regrowth when administered with irradn. in vivo at a dose of 0.4 mg/g. Tumor lung metastasis was inhibited by treatment with either TX-1877 or KIN-806 without irradn. at a dose of 0.4 mg/g. TX-1877 reduced markedly the mean no. of metastatic lung nodules in comparison with KIN-806. Moreover, TX-1877 and KIN-806 enhanced macrophage and helper T lymphocyte infiltration for 3 wk after drug treatment. TX-1877 shows a high EA value and has the C2 of HOMO localizing on N-methylamide and the C2 of LUMO localizing on 2-nitroimidazole group. The MO data might be useful for designing a bifunctional hypoxic cell radiosensitizer. TX-1877 and its analogs are potential antimetastatic hypoxic cell radiosensitizers, which would improve the efficiency of radiotherapy and quality of life in cancer treatment.
IT **220914-96-5P**, TX 1909

L11 ANSWER 11 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nitroimidazoleacetamides as antimetastatic hypoxic cell radiosensitizers)
RN 220914-96-5 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2-hydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)

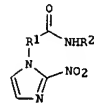


REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 12 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:137166 CAPLUS
DOCUMENT NUMBER: 134:178558
TITLE: Preparation of perfluorinated [18F]-radiolabeled nitroimidazole derivatives for cellular hypoxia detection.
INVENTOR(S): Marchand, Jacqueline; Gregoire, Vincent
PATENT ASSIGNEE(S): Universite Catholique de Louvain, Belg.
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012575	A1	20010222	WO 2000-EP4632	20000522
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1202945	A1	20020508	EP 2000-936775	20000522
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

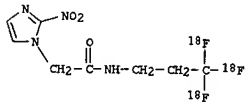
PRIORITY APPLN. INFO.: EP 1999-870172 A 19990811
WO 2000-EP4632 W 20000522
OTHER SOURCE(S): MARPAT 134:178558
GI



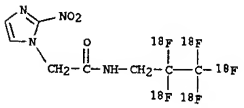
I

AB Title compds. (I; R1 = CH2; R2 = CHXCX2CY3; X = H, halo; Y = F), were prepd. for cellular hypoxia detection (no data). I preferably have an

L11 ANSWER 12 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
incorporation of [18F] atoms sufficient to give specific radioactivity of
1-30 Ci/mmol, preferably between 1-20 Ci/mmol, and most preferably 1-10
Ci/mmol. Tissue hypoxia in a patient is diagnosed by introducing I into a
patient, imaging tissue hypoxia in said patient, and quantifying tissue
hypoxia. Thus, [18F]-3,3,3-trifluoropropylamine was distd. and condensed
into a 0.degree. soln. of 2,3,5,6-tetrafluorophenyl 2-(2-nitroimidazol-1-
yl)acetate followed by stirring for 30 min. at 20.degree. to give 63%
[18F]-2-(2-nitro-1H-imidazol-1-yl)-N-(3,3,3-trifluoropropyl)acetamide.
IT **326590-99-2P 326591-00-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of perfluorinated [18F]-radiolabeled nitroimidazole derivs. for
cellular hypoxia detection)
RN 326590-99-2 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-[3,3,3-tri(fluoro-18F)propyl]-(9CI)
(CA INDEX NAME)



RN 326591-00-8 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-[2,2,3,3,3-penta(fluoro-18F)propyl]-(9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS

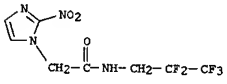
L11 ANSWER 12 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 13 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:113367 CAPLUS
DOCUMENT NUMBER: 135:134082
TITLE: Hypoxia in human intraperitoneal and extremity sarcomas
AUTHOR(S): Evans, S. M.; Hahn, S. M.; Magarelli, D. P.; Zhang, P.
J.; Jenkins, W. T.; Fraker, D. L.; Hsi, R. A.; McKenna, W. G.; Koch, C. J.
CORPORATE SOURCE: From the School of Veterinary Medicine, University of
Pennsylvania, Philadelphia, PA, USA
SOURCE: International Journal of Radiation Oncology, Biology,
Physics (2001), 49(2), 587-596
CODEN: IOBPD3; ISSN: 0360-3016
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The presence of hypoxia, measured by needle electrodes, was shown to be
assocd. with poor patient outcome in several human tumor types, including
soft tissue sarcomas. The present report emphasizes the evaluation of
hypoxia in soft tissue sarcomas based upon the binding of the
2-nitroimidazole drug EF5 (2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-
pentafluoropropyl) acetamide). EF5 has previously been shown to be
predictive of radiation response in animal tumors and in in vitro studies.
The authors have also previously reported studies of EF5 binding in human
squamous cell tumors. Using fluorescent immunohistochem. techniques, the
authors provide data on the presence and distribution of EF5 binding, as a
surrogate for hypoxia, in human spindle cell tumors. Patients with
spindle cell tumors who were scheduled for tumor surgery were asked to
participate in the phase I trial of EF5. Approx. 48 h preoperatively, EF5
was administered i.v. at doses between 9 and 21 mg/kg. Binding in frozen
sections of biopsied tissues was detd. using monoclonal antibodies labeled
with the green-excited, orange-emitting fluorescent dye, Cy3. Calibration
studies were performed in vitro by incubating fresh tumor tissue cubes
obtained from each patient with EF3 (an analog of EF5) under hypoxic
conditions ("ref. binding"). The goal of these calibration studies was to
quantify the maximal binding levels possible in individual patient's
tissues. The relationship between binding (in situ based on EF5 binding)
and ref. binding (in vitro based on EF3 binding) was detd. 8 Patients
were studied; 3 of these patients had gastrointestinal stromal tumors
(GIST). The incubation of tumor tissue cubes in EF3 under hypoxic
conditions demonstrated that all tumors bound drug to a similar extent.
Ref. binding showed a 3.2-fold variation in median fluorescence (113-356)
on an abs. fluorescence scale, calibrated by a Cy3 dye std. In situ
binding in the brightest tumor section varied by a factor of 25.4 between
the lowest and highest binding tumor (7.5-190.2). Heterogeneity of
highest binding was greater between tumors than within individual tumors.
A correspondence between EF5 binding and Eppendorf needle electrode
studies was seen in the 5 patients with non-GISTs. Inter- and
intratumoral heterogeneity of EF5 binding in spindle cell tumors was
documented. Patterns of binding consistent with diffusion limited hypoxia
are present in human spindle cell neoplasms.

IT **152721-37-4**, EF5
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST
(Analytical study); BIOL (Biological study); USES (Uses)
(hypoxia anal. in sarcomas by immunohistochem. using EF5)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-(9CI)
(CA INDEX NAME)



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

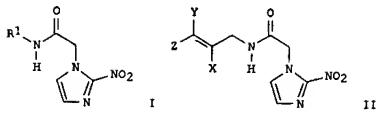
L11 ANSWER 14 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:78365 CAPLUS
DOCUMENT NUMBER: 134:147601
TITLE: Preparation of fluorinated nitroimidazole compounds and their labeled counterparts for the detection of hypoxia
INVENTOR(S): Dolbier, William R.; Li, An-Rong; Koch, Cameron J.; Kachur, Alexander V.
PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania, USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

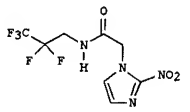
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007414	A1	20010201	WO 2000-US40437	20000720
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1202973	A1	20020508	EP 2000-960168	20000720
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

PRIORITY APPLN. INFO.: US 1999-144747P P 19990721
WO 2000-US40437 W 20000720

GI



I II

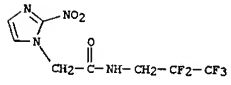


III

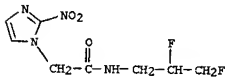
AB Methods for prepg. novel fluorinated nitroimidazoles I [R1 = CH2CHFCH2F, CH2CHFCHF2, CH2CHFCF3, CH2CH2CH2F, CH2CF2CHF2, and CH2CF2CF3], their 18F-labeled counterparts [at least one F is 18F], along with their corresponding intermediates II [X, Y, and Z are independently H or F] are disclosed. Thus, III (EF5) was prepd. by fluorination of the allyl precursor 2-(2-nitro-1H-imidazol-1-yl)-N-(2,3,3-trifluoroallyl)acetamide (II; X = Y = Z = F). The title compds. are disclosed as agents for non-invasive imaging techniques, such as PET, for detecting tissue hypoxia and demonstrated in PET imaging of a tumor-bearing rat treated with [18F]-labeled EF5. Diagnostic kits useful in practicing the methods of claimed invention are also provided.

IT **152721-37-4P 322637-51-4P 322637-52-5P 322637-53-6P 322637-54-7P 322637-55-8P 322637-56-9P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of fluorinated nitroimidazoles and their labeled counterparts as medical imaging agents for the detection of hypoxia)

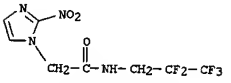
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-(9CI)
(CA INDEX NAME)



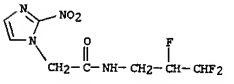
RN 322637-51-4 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2,3-difluoropropyl)-2-nitro-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



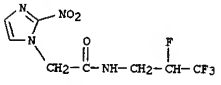
RN 322637-52-5 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



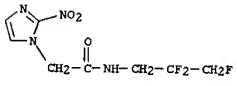
RN 322637-53-6 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,3,3-trifluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



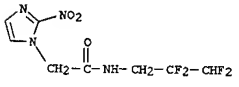
RN 322637-54-7 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,3,3,3-tetrafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



RN 322637-55-8 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3-trifluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



RN 322637-56-9 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3-tetrafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)

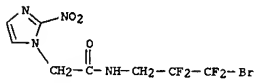


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

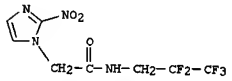
L11 ANSWER 15 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:806871 CAPLUS
DOCUMENT NUMBER: 134:207753
TITLE: [18F]-EF5, a marker for PET detection of hypoxia: synthesis of precursor and a new fluorination procedure
AUTHOR(S): Dolbier, W. R.; Li, A.-R.; Koch, C. J.; Shiue, C.-Y.; Kachur, A. V.
CORPORATE SOURCE: Department of Chemistry, University of Florida, Gainesville, FL, 32611, USA
SOURCE: Applied Radiation and Isotopes (2000), Volume Date 2001, 54(1), 73-80
CODEN: ARISEF; ISSN: 0969-8043
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:207753
AB There is a great deal of clin. and exptl. interest in detg. tissue hypoxia using non-invasive imaging methods. The authors have previously developed EF5, 2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide, with both invasive and non-invasive hypoxia detection in mind. EF5 and other 2-nitroimidazoles are used to detect hypoxia, because the rate of their bioreductive metab. is inversely dependent on oxygen partial pressure. Such metab. leads to the formation of covalent adducts within the metabolizing cells. Previously, the authors have described the invasive detection of these adducts by highly specific monoclonal antibodies after tissue biopsy. In this work, the authors synthesized 18F-labeled EF5, [18F]-2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide, in greater than 10% yield by direct fluorination of the newly synthesized precursor 2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,3,3-trifluoroallyl)acetamide by [18F]-F2 in trifluoroacetic acid. The objective was to optimize the electrophilic fluorination of the fluorinated alkene bond with fluorine gas, a new method of 18F-labeling of polyfluorinated mols. Previous biodistribution studies in mice have demonstrated uniform access of EF5 to all tissues with bioelimination dominated by renal excretion. When [18F]-EF5 was injected into a rat followed by urine collection and anal., the authors found no detectable metab. to other radioactive compds. Thus, [18F]-EF5 should be well suited for use as a non-invasive hypoxia marker with detection using positron emission tomog. (PET).
IT **328386-75-0P**

L11 ANSWER 15 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

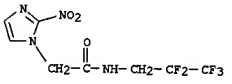
L11 ANSWER 15 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(using electrophilic fluorination in acidic medium to prep. [18F]-EF5, marker for PET detection of hypoxia)
RN 328386-75-0 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-bromo-2,2,3,3-tetrafluoropropyl)-2-nitro- (9CI) (CA INDEX NAME)



IT **152721-37-4P**, EF5
RL: SPN (Synthetic preparation); PREP (Preparation)
(using electrophilic fluorination in acidic medium to prep. [18F]-EF5, marker for PET detection of hypoxia)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)

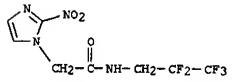


IT **322637-52-5P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(using electrophilic fluorination in acidic medium to prep. [18F]-EF5, marker for PET detection of hypoxia)
RN 322637-52-5 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



L11 ANSWER 16 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:248505 CAPLUS
DOCUMENT NUMBER: 133:29066
TITLE: Detection of hypoxia in human squamous cell carcinoma by EF5 binding
AUTHOR(S): Evans, Sydney M.; Hahn, Stephen; Pook, Deirdre R.; Jenkins, W. Timothy; Chalian, Ara A.; Zhang, Paul; Stevens, Craig; Weber, Randall; Weinstein, Gregory; Benjamin, Ivor; Mirza, Natasha; Morgan, Mark; Rubin, Steven; McKenna, W. Gillies; Lord, Edith M.; Koch, Cameron J.
CORPORATE SOURCE: Schools of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: Cancer Research (2000), 60(7), 2018-2024
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Localization and quantitation of 2-nitroimidazole drug binding in low pO2 tumors is a technique that can allow the assessment of hypoxia as a predictive assay. EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide] is such a drug, and it has been shown to be predictive of radiation response in rodent tumors. Using fluorescence immunohistochem. techniques, data on the presence, distribution, and levels of EF5 binding as a surrogate for hypoxia in human head and neck and uterine cervix squamous-cell cancers (SCCs) are provided. Six patients with SCC were studied. Four patients had head and neck tumors, and two had uterine cervix cancers. The incubation of fresh tissue cubes in EF3 under hypoxic conditions ("ref. binding") demonstrated that all tumors were capable of binding drug, and that this binding varied by a factor of 2.9-fold (174.5-516.1) on an abs. fluorescence scale. In the five patients treated at the lowest drug doses (9 mg/kg), in situ binding was quantifiable. For all six patients, the max. rate of in situ binding varied by a factor of 6.7 between the lowest and highest binding tumor (24.8-160.3) on an abs. fluorescence scale. In tumors with high binding regions, intratumoral heterogeneity was large, extending from minimal fluorescence (<1%) up to 88.6% of ref. binding. In tumors with minimal binding, there was little intratumoral heterogeneity. These studies demonstrate substantial heterogeneity of in situ binding between and within individual squamous-cell tumors.
IT **152721-37-4**, EF5
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process);

L11 ANSWER 16 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
USES (Uses)
(detection of hypoxia in human squamous-cell carcinoma by EF5 binding)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-(9CI)
(CA INDEX NAME)

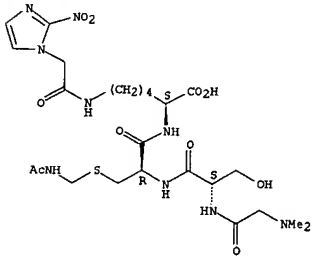


REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 17 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:243597 CAPLUS
DOCUMENT NUMBER: 133:55392
TITLE: Targeting Hypoxia in Tumors Using 2-Nitroimidazoles with Peptidic Chelators for Technetium-99m: Effect of Lipophilicity
AUTHOR(S): Zhang, Xiuguo; Su, Zi-Fen; Ballinger, James R.; Rauth, A. M.; Pollak, Alfred; Thornback, John R.
CORPORATE SOURCE: Division of Experimental Therapeutics, Ontario Cancer Institute, Toronto, ON, M5G 2M9, Can.
SOURCE: Bioconjugate Chemistry (2000), 11(3), 401-407
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tumor hypoxia is an important prognostic factor for response to therapy.
Radiolabeled 2-nitroimidazoles have been used for imaging hypoxia, and the
octanol/water partition coeff. (P) of these compds. appears to play a crucial role in their suitability for imaging. A series of 11
2-nitroimidazoles coupled to peptidic chelators for 99mTc with divergent P
was developed and evaluated in an in vitro system. Two classes of N3S
chelators were used: dialkyl-Gly-Ser-Cys-linker-2-nitroimidazole (Class I)
and dialkyl-Gly-Lys(2-nitroimidazole)-Cys (Class II). The chelators were
prepd. by automated solid-phase peptide synthesis. Xanthine oxidase was
able to reduce the 2-nitroimidiazole moiety on the ligands, but the rate
of redn. varied 5-fold among the different chelators. The chelators were
labeled by transchelation from [99mTc]gluconate at temps. between 22 and
100 .degree.C. The reaction mixts. were analyzed by HPLC and their P
values detd. The accumulation of each complex in suspension cultures of
Chinese hamster ovary cells incubated under aerobic or extremely hypoxic
conditions was detd. Radiochem. yields ranged from 5 to 80% for the 11
compds. HPLC showed that some of the compds. formed two complexes with
99mTc, possibly syn and anti conformations with respect to the Tc:O bond.
In general, the Class I chelators labeled more readily than the class II
chelators. The P values of the 99mTc complexes varied from 0.0002 to 5
and were generally in accordance with predictions based on structure.
There were also differences in P as a function of pH; the free acids had a

L11 ANSWER 17 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
lower P at pH 7.4 than at pH 2.0 due to ionization, whereas the amides did
not show this effect. Accumulation levels in aerobic cells were related
to P but varied over a narrow range. Four of the 11 compds. showed selective accumulation in hypoxic cells. The peptidic class of
2-nitroimidazoles, with flexible design and convenient solid-phase synthesis, deserves further study as agents for imaging hypoxia in tumors.
IT **248249-24-3DP**, 99mTc-labeled **276878-98-9DP**, 99mTc-labeled **276878-99-0DP**, 99mTc-labeled **276879-00-6DP**, 99mTc-labeled **276879-01-7DP**, 99mTc-labeled **276879-02-8P** **276879-03-9DP**, 99mTc-labeled **276879-04-0DP**, 99mTc-labeled **276879-05-1DP**, 99mTc-labeled
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP
(Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP
(Preparation); PROC (Process)
(targeting hypoxia in tumors using 2-nitroimidazoles with peptidic chelators for technetium-99m)
RN 248249-24-3 CAPLUS
CN L-Lysine, N,N-dimethylglycyl-L-seryl-S-[(acetylamino)methyl]-L-cysteinyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

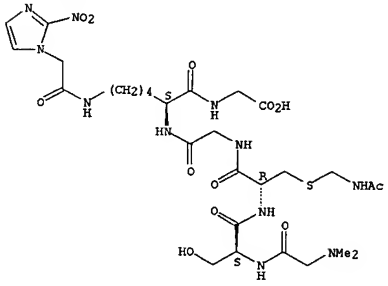
Absolute stereochemistry.



RN 276878-98-9 CAPLUS
CN Glycine, N,N-dimethylglycyl-L-seryl-S-[(acetylamino)methyl]-L-cysteinylglycyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysyl- (9CI) (CA INDEX NAME)

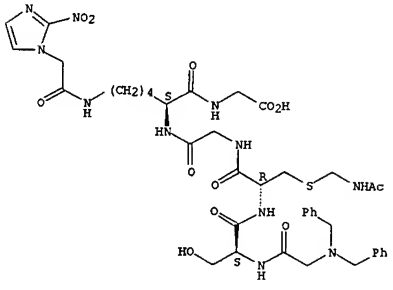
Absolute stereochemistry.

L11 ANSWER 17 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 276878-99-0 CAPLUS
CN Glycine, N,N-bis(phenylmethyl)glycyl-L-seryl-S-[(acetylamino)methyl]-L-cysteinylglycyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysyl- (9CI) (CA INDEX NAME)

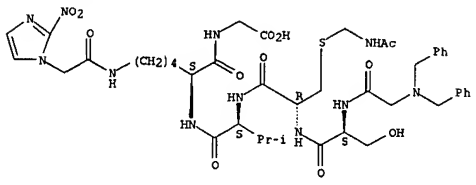
Absolute stereochemistry.



RN 276879-00-6 CAPLUS
CN Glycine, N,N-bis(phenylmethyl)glycyl-L-seryl-S-[(acetylamino)methyl]-L-

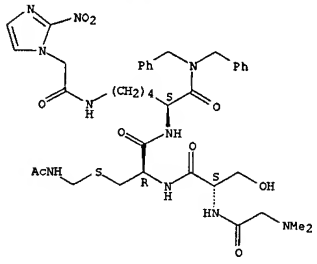
L11 ANSWER 17 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
cysteinyl-L-valyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysyl-
(9CI)
(CA INDEX NAME)

Absolute stereochemistry.



RN 276879-01-7 CAPLUS
CN L-Lysinamide, N,N-dimethylglycyl-L-seryl-S-[(acetylamino)methyl]-L-
cysteinyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-N,N-bis(phenylmethyl)-
(9CI) (CA INDEX NAME)

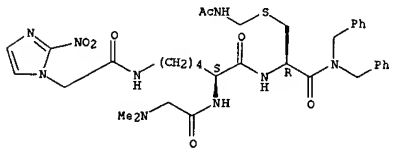
Absolute stereochemistry.



RN 276879-02-8 CAPLUS
CN L-Cysteine,
N,N-dimethylglycyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-
lysyl-S-[(acetylamino)methyl]- (9CI) (CA INDEX NAME)

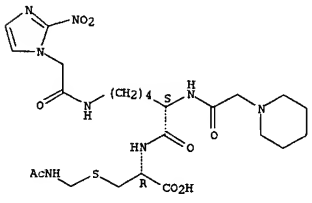
Absolute stereochemistry.

L11 ANSWER 17 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 276879-05-1 CAPLUS
CN L-Cysteine,
N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-N2-(1-piperidinylacetyl)-
L-lysyl-S-[(acetylamino)methyl]- (9CI) (CA INDEX NAME)

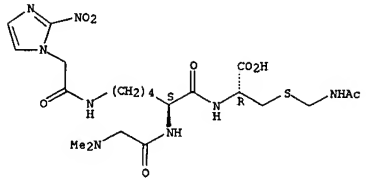
Absolute stereochemistry.



IT **276879-06-2DP**, 99mTc-labeled **276879-07-3DP**,
99mTc-labeled
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(targeting hypoxia in tumors using 2-nitroimidazoles with peptidic
chelators for technetium-99m)
RN 276879-06-2 CAPLUS
CN L-Cysteine, N,N-bis(phenylmethyl)glycyl-N6-[(2-nitro-1H-imidazol-1-
yl)acetyl]-L-lysyl-S-[(acetylamino)methyl]- (9CI) (CA INDEX NAME)

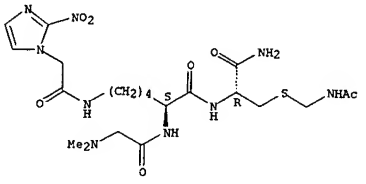
Absolute stereochemistry.

L11 ANSWER 17 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 276879-03-9 CAPLUS
CN L-Cysteinamide,
N,N-dimethylglycyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-
lysyl-S-[(acetylamino)methyl]- (9CI) (CA INDEX NAME)

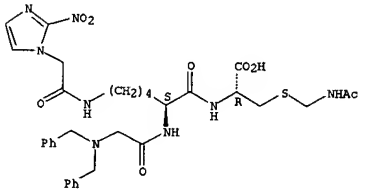
Absolute stereochemistry.



RN 276879-04-0 CAPLUS
CN L-Cysteinamide,
N,N-dimethylglycyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-
lysyl-S-[(acetylamino)methyl]-N,N-bis(phenylmethyl)- (9CI) (CA INDEX
NAME)

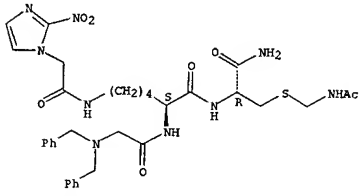
Absolute stereochemistry.

L11 ANSWER 17 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 276879-07-3 CAPLUS
CN L-Cysteinamide,
N,N-bis(phenylmethyl)glycyl-N6-[(2-nitro-1H-imidazol-1-
yl)acetyl]-L-lysyl-S-[(acetylamino)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR
THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

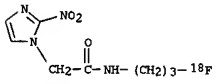
L11 ANSWER 18 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:135450 CAPLUS
DOCUMENT NUMBER: 133:55383
TITLE: Noninvasive detection of tumor hypoxia using the 2-nitroimidazole [18F]EF1
AUTHOR(S): Evans, Sydney M.; Kachur, Alexander V.; Shiue, Chyng-Yann; Hustinx, Roland; Jenkins, W. Timothy; Shive, Grace G.; Karp, Joel S.; Alavi, Abass; Lord, Edith M.; Dolbier, William R., Jr.; Koch, Cameron J.
CORPORATE SOURCE: Schools of Medicine and Veterinary Medicine, University of Pennsylvania, Philadelphia, PA, USA
SOURCE: Journal of Nuclear Medicine (2000), 41(2), 327-336
CODEN: JNMEAQ; ISSN: 0161-5505
PUBLISHER: Society of Nuclear Medicine, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The noninvasive assessment of tumor hypoxia in vivo is under active investigation because hypoxia has been shown to be an important prognostic factor for therapy resistance. Various nuclear medicine imaging modalities are being used, including PET imaging of 18F-contg. compds. In this study, we report the development of 18F-labeled EF1 for noninvasive imaging of hypoxia. EF1 is a 3-monofluoro analog of the well-characterized hypoxia marker EF5, 2(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide, which has been used to detect hypoxia in tumor and nontumor systems using immunohistochem. methods. We have studied 2 rat tumor types: the hypoxic Morris 7777 (Q7) hepatoma and the oxic 9LF glioma tumor, each grown in s.c. sites. PET studies were performed using a pharmacol. dose of nonradioactive carrier in addn. to [18F]EF1 to optimize and assess drug biodistribution. After PET imaging of the tumor-bearing rats, tissues were obtained for .gamma.-counting of the 18F in various tissues and immunohistochem. detection of intracellular drug adducts in tumors. In one pair of tumors, Eppendorf needle electrode studies were performed. [18F]EF1 was excreted dominantly through the urinary tract. The tumor-to-muscle (T/M) ratio of [18F]EF1 in the Q7 tumors was 2.7 and 2.4 based on PET studies and 2.1, 2.5, and 3.0 based on .gamma.-counting of the tissues (n = 3). In contrast, the T/M ratio of [18F]EF1 in the 9LF glioma tumor was 0.8 and 0.5 based on PET studies and 1.0, 1.2, and 1.4 based on .gamma.-counting of the tissues (n = 3). Immunohistochem. anal. of drug adducts for the two tumor types agreed with

L11 ANSWER 18 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
the radioactivity anal. In the Q7 tumor, substantial heterogeneous binding was obsd. throughout the tumor, whereas in the 9LF tumor minimal binding was found. [18F]EF1 is an excellent radiotracer for noninvasive imaging of tumor hypoxia.

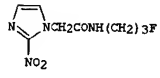
IT **252736-29-1**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(detection of tumor hypoxia using 2-nitroimidazole [18F]EF1)

RN 252736-29-1 CAPLUS
CN 1H-Imidazole-1-acetamide, N-[3-(fluoro-18F)propyl]-2-nitro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 19 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:719194 CAPLUS
DOCUMENT NUMBER: 132:49925
TITLE: Synthesis of new hypoxia markers EF1 and [18F]-EF1
AUTHOR(S): Kachur, Alexander V.; Dolbier, William R., Jr.; Evans, Sydney M.; Shiue, Chyng-Yann; Shiue, Grace G.; Skov, Kirsten A.; Baird, Ian R.; James, Brian R.; Li, An-Rong; Roche, Alex; Koch, Cameron J.
CORPORATE SOURCE: Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: Applied Radiation and Isotopes (1999), 51(6), 643-650
CODEN: ARISEF; ISSN: 0969-8043
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



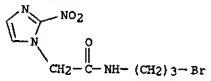
I

AB We report on the prepn. of a hypoxia marker 2-(2-nitroimidazol-1[H]-yl)-N-(3-fluoropropyl)acetamide (EF1, I) and its 18F analog. Two methods for the prepn. of 3-fluoropropylamine, the EF1 side chain, are described. [18F]-EF1 was prepd. with a radiochem. yield of 2% by nucleophilic substitution of bromine in 2-(2-nitroimidazol-1[H]-yl)-N-(3-bromopropyl)acetamide (EBr1) by carrier-added 18F in DMSO at 120.degree.. Our results demonstrate the prepn. of clin. relevant amts. of [18F]-EF1 for use as a non-invasive hypoxia marker with detection using positron emission tomog.

IT **252736-27-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction with fluoride)

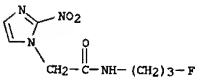
RN 252736-27-9 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-bromopropyl)-2-nitro- (9CI) (CA INDEX NAME)

L11 ANSWER 19 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

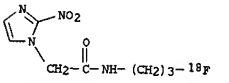


IT **252736-28-0P 252736-29-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 252736-28-0 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-fluoropropyl)-2-nitro- (9CI) (CA INDEX NAME)

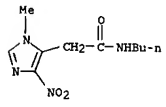


RN 252736-29-1 CAPLUS
CN 1H-Imidazole-1-acetamide, N-[3-(fluoro-18F)propyl]-2-nitro- (9CI) (CA INDEX NAME)



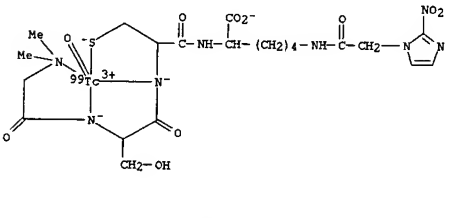
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 20 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:612558 CAPLUS
DOCUMENT NUMBER: 132:3337
TITLE: Investigations on imidazoles. 99. Synthesis and some conversions of esters of 4-nitro-5-imidazolylmalonic, -acetoacetic, and -cyanoacetic acids
AUTHOR(S): Kochergin, P. M.; Reznichenko, L. A.; Gireva, R. N.; Aleksandrova, E. V.
CORPORATE SOURCE: Center for Drug Chemistry, All-Russian Research Institute for Pharmaceutical Chemistry, Moscow, 119815, Russia
SOURCE: Chemistry of Heterocyclic Compounds (New York) (Translation of Khimiya Geterotsiklicheskikh Soedinenii) (1999), 35(1), 51-57
CODEN: CHCCAL; ISSN: 0009-3122
PUBLISHER: Consultants Bureau
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 132:3337
AB Title esters of 1-alkyl(1,2-dialkyl)-4-nitro-5-imidazolylmalonic, -acetoacetic, and -cyanoacetic acids were prepd. by treating 5-chloro(bromo)-1-alkyl(1,2-dialkyl)-4-nitroimidazoles with Et esters of carboxylic acids indicated. Some conversions of the compds. obtained have been studied, including ketone and acid decompn., synthesis of derivs. at the CO2H and CO groups, and hydrogenation to 4-aminoimidazole derivs.
IT **251297-89-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reactions of esters of nitroimidazolylmalonic, -acetoacetic, and -cyanoacetic acids)
RN 251297-89-9 CAPLUS
CN 1H-Imidazole-5-acetamide, N-butyl-1-methyl-4-nitro- (9CI) (CA INDEX NAME)



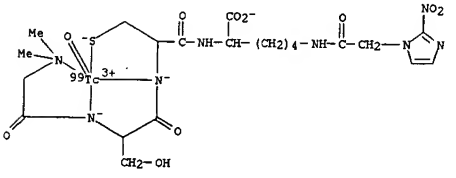
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 21 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:539032 CAPLUS
DOCUMENT NUMBER: 131:319697
TITLE: Synthesis and Evaluation of Two Technetium-99m-Labeled Peptidic 2-Nitroimidazoles for Imaging Hypoxia
AUTHOR(S): Su, Zi-Fen; Zhang, Xiuguo; Ballinger, James R.; Rauth, A. M.; Pollak, Alfred; Thornback, John R.
CORPORATE SOURCE: Departments of Medical Biophysics and Pharmaceutical Sciences, University of Toronto, Toronto, ON, M5G 2M9, Can.
SOURCE: Bioconjugate Chemistry (1999), 10(5), 897-904
CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The presence of hypoxic cells in solid tumors is a marker for therapy-resistant, aggressive disease. The noninvasive detection of hypoxic cells in tumors by radiolabeled 2-nitroimidazoles is a diagnostic technique under current evaluation. Two peptidic agents, dimethylglycyl-L-seryl-L-cysteinyl-lysyl{N.epsilon.-[1-(2-nitro-1H-imidazolyl)acetamido]}glycine (RP435) and dimethylglycyl-tert-butylglycyl-L-cysteinyl-glycine-[2-(2-nitro-1H-imidazolyl)ethyl]amide (RP535) have been synthesized. Both agents contain an N3S class chelator for 99mTc and Re and a 2-nitroimidazole group which can be enzymically reduced and selectively trapped in cells under hypoxic conditions. Two isomers of 99mTcO-RP435, which are assumed to be syn and anti conformations, were obsd. on HPLC anal. The interconversion of the two isomers in aq. soln. was investigated. In contrast, RP535 chelated 99mTc to form a single isomer and no conversion to its counterpart has been obsd. on HPLC anal. The tert-Bu group on the chelator may inhibit the formation and interconversion of the syn and anti isomers of 99mTcO-RP535. Both tracers showed a significant degree of hypoxia-specific accumulation in an in vitro assay, with 99mTcO-RP535 showing higher selectivity for hypoxic cells than 99mTcO-RP435. These results suggest that 99mTcO-RP535 represents a lead compd. worthy of further investigation as an agent for imaging hypoxia in tumors.
IT **247909-46-2P**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(synthesis and evaluation of technetium-99m-labeled peptidic 2-nitroimidazoles for imaging hypoxia)
RN 247909-46-2 CAPLUS
CN Technetate(1-)-99Tc, [N,N-dimethylglycyl-.kappa.N-L-seryl-.kappa.N-L-cysteinyl-.kappa.N,.kappa.S-.kappa.N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysinato(4-)]oxo-, hydrogen, (SP-5-25-) (9CI) (CA INDEX NAME)



● H+

IT **247909-38-2P 247909-39-3P**
RL: PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(synthesis and evaluation of technetium-99m-labeled peptidic 2-nitroimidazoles for imaging hypoxia)
RN 247909-38-2 CAPLUS
CN Technetate(1-)-99Tc, [N,N-dimethylglycyl-.kappa.N-L-seryl-.kappa.N-L-cysteinyl-.kappa.N,.kappa.S-.kappa.N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysinato(4-)]oxo-, hydrogen, (SP-5-25-A)- (9CI) (CA INDEX NAME)



● H+

RN 247909-39-3 CAPLUS
CN Technetate(1-)-99Tc, [N,N-dimethylglycyl-.kappa.N-L-seryl-.kappa.N-L-

L11 ANSWER 21 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
lysinato(4-)]oxo-, hydrogen, (SP-5-25)- (9CI) (CA INDEX NAME)

● H+

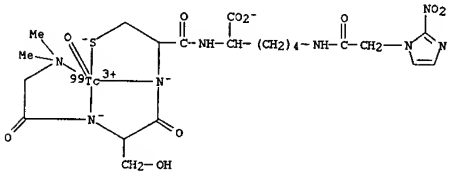
IT **247909-38-2P 247909-39-3P**
RL: PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(synthesis and evaluation of technetium-99m-labeled peptidic 2-nitroimidazoles for imaging hypoxia)
RN 247909-38-2 CAPLUS
CN Technetate(1-)-99Tc, [N,N-dimethylglycyl-.kappa.N-L-seryl-.kappa.N-L-cysteinyl-.kappa.N,.kappa.S-.kappa.N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysinato(4-)]oxo-, hydrogen, (SP-5-25-A)- (9CI) (CA INDEX NAME)

● H+

RN 247909-39-3 CAPLUS
CN Technetate(1-)-99Tc, [N,N-dimethylglycyl-.kappa.N-L-seryl-.kappa.N-L-

L11 ANSWER 21 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

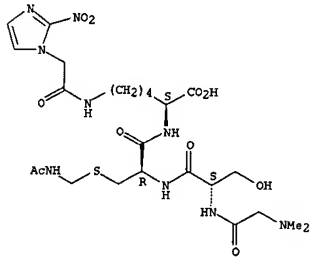
cysteinyl-.kappa.N,.kappa.S-.kappa.N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysinato(4-)]oxo-, hydrogen, (SP-5-25-C)- (9CI) (CA INDEX NAME)



● H+

IT **248249-24-3P**, RP 435
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and evaluation of technetium-99m-labeled peptidic 2-nitroimidazoles for imaging hypoxia)
RN 248249-24-3 CAPLUS
CN L-Lysine, N,N-dimethylglycyl-L-seryl-S-[(acetylamino)methyl]-L-cysteinyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

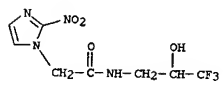
Absolute stereochemistry.



L11 ANSWER 21 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

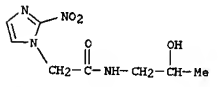
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS
FORMAT RECORD. ALL CITATIONS AVAILABLE IN THE RE

L11 ANSWER 22 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:284037 CAPLUS
DOCUMENT NUMBER: 131:15726
TITLE: Preclinical development and current status of the fluorinated 2-nitroimidazole hypoxia probe N-(2-hydroxy-3,3,3-trifluoropropyl)-2-(2-nitro-1-imidazolyl)acetamide (SR 4554, CRC 94/17): a non-invasive diagnostic probe for the measurement of tumor hypoxia by magnetic resonance spectroscopy and imaging, and by positron emission tomography. [Erratum to document cited in CA129:341244]
AUTHOR(S): Aboagye, Eric O.; Kelson, Andrew B.; Tracy, Michael; Workman, Paul
CORPORATE SOURCE: Dep. Radiol.-MR Res., The Johns Hopkins Univ. School Medicine, Baltimore, MD, 21205, USA
SOURCE: Anti-Cancer Drug Design (1998), 13(8), 1009-1010 CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB The correct structure of the 2-nitroimidazole, EF5, is given.
IT **167648-73-9P**, SR 4554
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(preclin. development and current status of the fluorinated 2-nitroimidazole hypoxia probe SR 4554, a non-invasive diagnostic probe for the measurement of tumor hypoxia (Erratum))
RN 167648-73-9 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)- (9CI) (CA INDEX NAME)



L11 ANSWER 23 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:5874 CAPLUS
DOCUMENT NUMBER: 130:206754
TITLE: TX-1877: design, synthesis, and biological activities as a BRM-functional hypoxic cell radiosensitizer
AUTHOR(S): Kasai, Soko; Nagasawa, Hideko; Kuwasaka, Hideki; Oshodani, Tomoko; Nishioka, Akihito; Ogawa, Yasuhiro; Yoshida, Shoji; Inayama, Seiichi; Inomata, Taisuke; Hori, Hitoshi
CORPORATE SOURCE: Department of Biological Science and Technology, Faculty of Engineering, The University of Tokushima, Tokushima, 770-8506, Japan
SOURCE: International Journal of Radiation Oncology, Biology, Physics (1998), 42(4), 799-802 CODEN: IOBPD3; ISSN: 0360-3016
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 2-Nitroimidazole acetamide TX-1877 and its derivs. (TX-1877 analogs) were designed, synthesized, and evaluated by their in vitro and in vivo radiosensitization, tumor growth control, suppression of lung metastasis, and immunopotentiation, as biol. response modifier (BRM)-functional hypoxic cell radiosensitizers. TX-1877 analogs were designed and synthesized in our lab. In vitro radiosensitizing ability was estd. using EMT6/KU cells under hypoxic conditions. In vivo radiosensitization, antimetastasis, and immunopotentiation were evaluated using female C3H/He mice bearing the SCCVII tumor. Days (15 or 10) after the inoculation of 105 SCCVII tumor cells into the hinder thigh, a drug (0.4 mg/g) was administered i.p. and local irradn. of 30 Gy was given at 30 min after its administration. Tumor growth was obsd. for 20 days and mice were euthanized to count the no. of metastatic nodules on the surface of the lungs. Tumor tissues were extirpated and stained by the ABC method at 1, 2, and 3 wk after treatment for immunol. evaluation. Novel types of bifunctional radiosensitizers, TX-1877 and its analogs possessing BRM-functions (i.e., antimetastatic and immunopotentiation effects) were developed. In vitro radiosensitizing abilities of TX-1877 and its analogs, with their partition coeff. values of more than 0.050, were comparable to misonidazole (MISO) at their doses of 1 mM. Tumor regrowth was suppressed evidently 20 days after the treatment in the irradiated group with TX-1877 (TX-1877 plus R) and with KIN-806 (KIN-806 plus R).

L11 ANSWER 23 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
The former group reduced markedly the mean no. of metastatic lung nodules regardless of radiation therapy. TX-1877 and KIN-806 plus R induced helper T lymphocytes. The TX-1877, TX-1877 plus R, KIN-806, and KIN-806 plus R enhanced macrophage infiltration for 3 wk after treatment. TX-1877 is an excellent BRM-functional hypoxic cell radiosensitizer, expected to be useful for clin. use.
IT **220914-96-5P**, TX 1909
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(design, synthesis, and biol. activities of TX-1877 analogs as BRM-functional hypoxic cell radiosensitizers)
RN 220914-96-5 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2-hydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS
FORMAT RECORD. ALL CITATIONS AVAILABLE IN THE RE

L11 ANSWER 24 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:622782 CAPLUS
DOCUMENT NUMBER: 129:341244
TITLE: Preclinical development and current status of the fluorinated 2-nitroimidazole hypoxia probe N-(2-hydroxy-3,3,3-trifluoropropyl)-2-(2-nitro-1-imidazolyl) acetamide (SR 4554, CRC 94/17): a non-invasive diagnostic probe for the measurement of tumor hypoxia by magnetic resonance spectroscopy and imaging, and by positron emission tomography
AUTHOR(S): Aboagye, Eric O.; Kelson, Andrew B.; Tracy, Michael; Workman, Paul
CORPORATE SOURCE: Dep. Radiol.-MR Res., The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Anti-Cancer Drug Design (1998), 13(6), 703-730
CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

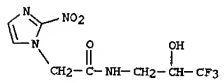
AB A review with many refs. Hypoxia occurs to a variable extent in a vast majority of rodent and human solid tumors. It results from an inadequate and disorganized tumor vasculature, and hence an impaired oxygen delivery. A probe for the non-invasive detection of tumor hypoxia could find important utility in the selection of patients for therapy, with bioreductive agents, anti-angiogenic/anti-vascular therapies and hypoxia-targeted gene therapy. In addn., tumor hypoxia has been shown to predict for treatment outcome following radio- or chemotherapy in human cancers, the underlying mechanism for which may involve hypoxia driving genetic instability and resulting tumor progression. Beyond oncol., utility can also be envisaged in stroke, ischemic heart disease, peripheral vascular disease, arthritis and other disorders. Design, validation, preclin. development and current status of a fluorinated 2-nitroimidazole, N-(2-hydroxy-3,3,3-trifluoropropyl)-2-(2-nitro-1-imidazolyl) acetamide (SR 4554, CRC 94/17), which has been rationally designed for the measurement of tumor hypoxia by magnetic resonance spectroscopy (MRS) and imaging (MRI), are reviewed. Application in positron emission tomog. (PET) detection is also proposed. Design goals were: (i) a nitro group with appropriate redox potential for selective redn. and binding in hypoxic tumor cells; (ii) hydrophilic/hydrogen bonding character in the side chain to limit nervous tissue penetration and prevent neurotoxicity; and (iii) three equiv. fluorine atoms to enhance MRS/MRI detection, located in a metabolically stable position. Redn. of SR 4554 by mouse liver microsomes was dependent on oxygen

L11 ANSWER 24 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

content, with a half-maximal inhibition at 0.48 .+-. 0.06%. SR 4554 underwent nitroredn. by hypoxic but not oxic tumor cells in vitro and electron energy loss spectroscopic anal. showed selective retention in the hypoxic regions of multicellular tumor spheroids. Pharmacokinetic design goals were met. In particular, low brain tissue concns. were seen in contrast to excellent tumor levels, as measured by high performance liq. chromatog. The extent of this restricted entry to brain tumor was surprising given the overall octanol/water partition coeff. and was attributed to the hydrophilic/ hydrogen bonding character of the side chain. Quant. MRS was used to assess the retention of 19F signal in murine tumors and human tumor xenografts. The 19F retention index (FRI; ratio of 19F signal levels at 6 h relative to that at 45 min) ranged from 0.5 to 1.0 and 0.2 to 0.9 for murine tumors and human xenografts resp. The correlation between SR 4554 retention and pO2 was not a linear one, but when FRI was >0.5, the % pO2 .ltoreq. 5 mmHg was always >60%, indicating that high FRI was assocd. with low levels of oxygenation. Finally, whole body 19F-MRI in mice demonstrated that SR 4554 and related metabolites localized mainly in tumor, liver and bladder regions. A selective MRS signal was readily detectable in tumors at doses at least 7-fold lower than those likely to cause toxicity in mice. We conclude that proof of principle is established for the use of SR 4554 as a non-invasive MRS/MRI probe for the detection of tumor hypoxia. Based on these promising studies, SR 4554 has been selected for clin. development.

IT **167648-73-9P**, SR 4554
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(preclin. development and current status of the fluorinated 2-nitroimidazole hypoxia probe SR 4554, a non-invasive diagnostic probe for the measurement of tumor hypoxia)

RN 167648-73-9 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)-(9CI) (CA INDEX NAME)



L11 ANSWER 24 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

REFERENCE COUNT: 99 THERE ARE 99 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

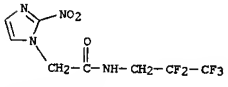
L11 ANSWER 25 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:589027 CAPLUS
DOCUMENT NUMBER: 129:260386
TITLE: An effective synthetic route to EF5
AUTHOR(S): Baird, Ian R.; Skov, Kirsten A.; James, Brian R.; Rettig, Steven J.; Koch, Cameron J.
CORPORATE SOURCE: Department of Chemistry, University of British Columbia, Vancouver, BC, V6T 1Z1, Can.
SOURCE: Synthetic Communications (1998), 28(19), 3701-3709
CODEN: SYNCAV; ISSN: 0039-7911
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB EF5 (a 2-nitroimidazole contg. an N-(pentafluoropropyl)acetamide substituent) is a very sensitive probe for quantifying the amt. of hypoxia within cells; a much improved, short step, synthetic procedure is described for EF5, whose X-ray structure is also presented.

IT **152721-37-4P**, EF5
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of (nitroimidazolyl)(pentafluoropropyl)acetamide)

RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-(9CI)
(CA INDEX NAME)

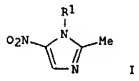


REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 26 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:184322 CAPLUS
DOCUMENT NUMBER: 128:286350
TITLE: 2-Methyl-5-nitroimidazoles and their use as inducers
for endogenous antitumor activity
INVENTOR(S): Sugawara, Tsutomu; Kagitani, Tsutomu
PATENT ASSIGNEE(S): Zaidanhojin Taishitsu Kenkyukai, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 10077272	A2	19980324	JP 1996-234421	19960904

PRIORITY APPLN. INFO.: JP 1996-234421 19960904
OTHER SOURCE(S): MARPAT 128:286350
GI



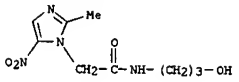
I

AB The title inducers contain 2-methyl-5-nitroimidazoles I [R1 = (CH2)a(CHOH)b(CH2)c[O(CH2)d]eH (a = 1-3; b, c = 0, 1; d = 0-3; e = 1-3; when d = 0, then e = 1), (CH2)fCO2(CH2)gH (f = 1-3; g = 0-3), (CH2)hCONH(CH2)i[O(CH2)j]kH (h = 1, 2; i = 0-6; j = 0-2; k = 0, 1)] as active ingredients and are administered at .ltoreq.1 mg/kg/time. Flagyl at 1 mg/kg/day for 20 days in total (10 days before and 10 days after inoculation of B16 melanoma cells) caused regression of the tumor cells in mice.

IT **205811-49-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 2-methyl-5-nitroimidazoles as inducers for endogenous antitumor activity)

RN 205811-49-0 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-hydroxypropyl)-2-methyl-5-nitro- (9CI) (CA INDEX NAME)

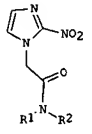
L11 ANSWER 26 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



L11 ANSWER 27 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:165453 CAPLUS
DOCUMENT NUMBER: 128:192653
TITLE: Preparation of fluorinated 2-nitroimidazole analogs
for detecting hypoxic tumor cells
INVENTOR(S): Tracy, Michael; Kelson, Andrew B.; Workman, Paul; Lewis, Alexander D.; Aboagye, Eric O.
PATENT ASSIGNEE(S): SRI International, USA
SOURCE: U.S., 24 pp., Cont.-in-part of U.S. Ser. No. 286,477, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5721265	A	19980224	US 1995-458178	19950602
CA 2196900	AA	19960215	CA 1995-2196900	19950731
WO 9604249	A1	19960215	WO 1995-US9611	19950731
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 775117	A1	19970528	EP 1995-927535	19950731
EP 775117	B1	20011121		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 10506104	T2	19980616	JP 1995-506660	19950731
AT 209187	E	20011215	AT 1995-927535	19950731
ES 2165430	T3	20020316	ES 1995-927535	19950731

PRIORITY APPLN. INFO.: US 1994-286477 B2 19940805
US 1995-458178 A 19950602
WO 1995-US9611 W 19950731
OTHER SOURCE(S): MARPAT 128:192653
GI

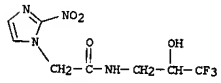


I

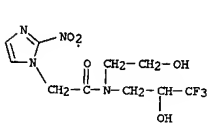
AB Title compds. I (R1, R2 = independently H, monosaccharide, alkyl, hydroxyalkyl, heterocycle) were prepd. to detect hypoxic tumor cells. Thus, I [R1 = H, R2 = CH2CH(OH)CF3] was prepd. and tested for detecting hypoxic tumor cells.

L11 ANSWER 27 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
IT **167648-73-9P 177595-17-4P 177595-20-9P 177595-21-0P 177595-22-1P 203452-63-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of fluorinated nitroimidazole analogs for detecting hypoxic tumor cells)

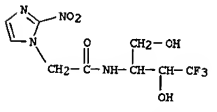
RN 167648-73-9 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)- (9CI) (CA INDEX NAME)



RN 177595-17-4 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2-hydroxyethyl)-2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)- (9CI) (CA INDEX NAME)

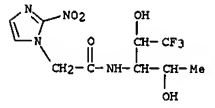


RN 177595-20-9 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-[3,3,3-trifluoro-2-hydroxy-1-(hydroxymethyl)propyl]- (9CI) (CA INDEX NAME)

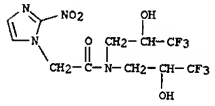


RN 177595-21-0 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-[3,3,3-trifluoro-2-hydroxy-1-(1-hydroxyethyl)propyl]- (9CI) (CA INDEX NAME)

L11 ANSWER 27 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

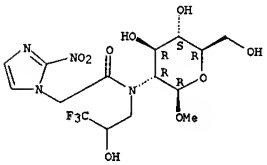


RN 177595-22-1 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N,N-bis(3,3,3-trifluoro-2-hydroxypropyl)- (9CI) (CA INDEX NAME)

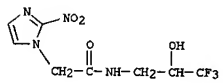


RN 203452-63-5 CAPLUS
CN .beta.-D-Glucopyranoside, methyl 2-deoxy-2-[[(2-nitro-1H-imidazol-1-yl)acetyl](3,3,3-trifluoro-2-hydroxypropyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

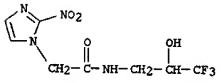


L11 ANSWER 28 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:87382 CAPLUS
DOCUMENT NUMBER: 128:202680
TITLE: The relationship between tumor oxygenation determined by oxygen electrode measurements and magnetic resonance spectroscopy of the fluorinated 2-nitroimidazole SR-4554
AUTHOR(S): Aboagye, E. O.; Maxwell, R. J.; Horsman, M. R.; Lewis, A. D.; Workman, P.; Tracy, M.; Griffiths, J. R.
CORPORATE SOURCE: Beatson Laboratories, CRC Department of Medical Oncology, Glasgow, G61 1BD, UK
SOURCE: British Journal of Cancer (1998), 77(1), 65-70
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The relationship between two methods of assessing tumor oxygenation in vivo, namely oxygen electrode measurement and magnetic resonance spectroscopy (MRS) of the fluorinated 2-nitroimidazole SR-4554, was investigated. Using three tumor models (two sites), no linear correlation was obsd. between 19F retention index and pO2 parameters (r .ltoreq. 0.3). Substantial retention of SR-4554 (19F retention index > 0.5) was, however, assocd. with low tumor pO2 (% pO2 .ltoreq. 5 mmHg = 60%). Depending on the pO2 parameters used, SR-4554 administration was shown to produce either a significant or a non-significant increase in tumor oxygenation. The authors conclude that measurement of SR-4554-related compd.(s) by 19F-MRS has the potential to detect clin. relevant levels of tumor hypoxia.
IT **167648-73-9**, SR-4554
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified);
ANST (Analytical study); BIOL (Biological study); USES (Uses)
(relationship between tumor oxygenation detd. by oxygen electrode measurements and magnetic resonance spectroscopy of fluorinated 2-nitroimidazole SR-4554)
RN 167648-73-9 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)- (9CI) (CA INDEX NAME)



L11 ANSWER 29 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:752599 CAPLUS
DOCUMENT NUMBER: 128:70367
TITLE: Bioreductive metabolism of the novel fluorinated 2-nitroimidazole hypoxia probe N-(2-hydroxy-3,3,3-trifluoropropyl)-2-(2-nitroimidazolyl) acetamide (SR-4554)
AUTHOR(S): Aboagye, Eric O.; Lewis, Alexander D.; Tracy, Michael; Workman, Paul
CORPORATE SOURCE: CRC DEPARTMENT OF MEDICAL ONCOLOGY, CLINICAL PHARMACOLOGY AND NEW DRUG DEVELOPMENT TEAM, UNIVERSITY OF GLASGOW, GLASGOW, G61 1BD, UK
SOURCE: Biochemical Pharmacology (1997), 54(11), 1217-1224
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aim of this work was to study the metabolic characteristics of the novel fluorinated 2-nitroimidazole hypoxia probe N-(2-hydroxy-3,3,3-trifluoropropyl)-2-(2-nitroimidazolyl) acetamide (SR-4554). HPLC and 19F NMR methods were employed to evaluate the rate of reductive metab. of SR-4554 and the nature of the resulting metabolites, resp. SR-4554 was enzymically reduced by mouse liver microsomes (1.1 .+-. 0.1 nmol of SR-4554 reduced/min/mg protein), purified rat and human NADPH:cytochrome P 450 reductase (17.8 .+-. 0.4 and 5.0 .+-. 0.5 nmol of SR-4554 reduced/min/mg protein, resp.), and SCCVII tumor homogenates (2.3 .+-. 0.3 nmol of SR-4554 reduced/min/g tumor) under nitrogen. NADPH:cytochrome P 450 reductase was a major microsomal enzyme involved in the bioredn. of SR-4554 by liver microsomes. In a panel of murine and human tumor xenografts, cytochrome P 450 reductase activities were found to be low and only varied by 3-fold between different tumor types, suggesting that enzyme activities within the tumors are unlikely to influence markedly in vivo reductive metab. Redn. of SR-4554 by mouse liver microsomes showed a characteristic oxygen dependence with a half-maximal inhibition of 0.48 .+-. 0.06%. Thus, the reductive metab. of SR-4554 can be employed to detect the low oxygen tensions that occur within both murine and human tumors. Sol., low mol. wt. reductive metabolites of SR-4554 were identified by 19F NMR. These metabolite peaks appeared (up to 0.12 ppm) downfield of the parent drug peak. In conclusion, SR-4554 undergoes an

L11 ANSWER 29 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
oxygen-dependent metab. that involves NADPH:cytochrome P 450 reductase. 19F NMR is capable of identifying reduced metabolites that are undetectable by HPLC.
IT **167648-73-9**, SR-4554
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(bioreductive metab. of hypoxia probe SR-4554)
RN 167648-73-9 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)- (9CI) (CA INDEX NAME)



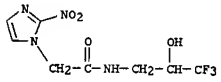
L11 ANSWER 30 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:497147 CAPLUS
DOCUMENT NUMBER: 127:202363
TITLE: Preclinical evaluation of the fluorinated 2-nitroimidazole N-(2-hydroxy-3,3,3-trifluoropropyl)-2-(2-nitro-1-imidazolyl)acetamide (SR-4554) as a probe for the measurement of tumor hypoxia
AUTHOR(S): Aboagye, Eric O.; Maxwell, Ross J.; Kelson, Andrew B.; Tracy, Michael; Lewis, Alexander D.; Graham, Martin A.; Horsman, Michael R.; Griffiths, John R.; Workman, Paul
CORPORATE SOURCE: Cancer Res. Campaign, Dep. Medical Oncology, Beatson Labs., Glasgow, G61 1BD, UK
SOURCE: Cancer Research (1997), 57(15), 3314-3318
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A novel probe, N-(2-hydroxy-3,3,3-trifluoropropyl)-2-(2-nitro-1-imidazolyl)acetamide (SR-4554), has been used to detect tumor hypoxia non-invasively by 19F magnetic resonance spectroscopy (19F MRS). The compd. was designed to undergo a hypoxia-dependent, one-electron redn. to metabolites that are selectively retained in tumors and has attractive pharmacokinetic, toxicol., and detection sensitivity properties. As a prelude to clin. studies, we report here for the first time on the ability to detect a MR signal following SR-4554 administration in various transplantable tumors and describe validation studies, consisting of a correlation between signal retention and radiobiol. hypoxic fraction, and the effects of modulating the degree of hypoxia by hydralazine and carbogen breathing. SR-4554 was absorbed and then eliminated from EMT6 tumors with a half-life of 51 min following an injection of 180 mg/kg i.p. of SR-4554. Using a quant. 19F MRS technique, the 19F retention index (19FRI; 19F signal level at 6 h/45 min) was detd. for four commonly used murine tumors (EMT6, SCCVII, KHT, and RIF-1). The retention of high tumor concns. of fluorinated probe at 6 h, despite the much lower (20-fold) concn. of parent SR-4554 detected by high-performance liq. chromatog., was consistent with the involvement of one or more nitroreduced metabolites and suggested that 19F MRS might give a quant. measure of tumor hypoxia.

L11 ANSWER 30 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

In these murine tumors, 19FRI correlated with the reported radiobiol. hypoxic fraction of the tumors (r = 0.988). In addn., changes in tumor microenvironment were detected by 19F MRS. An increase in hypoxia induced by hydralazine treatment of RIF-1 tumor-bearing mice was assocd. with a 2.4-fold increase in 19FRI compared to untreated controls. In contrast, carbogen breathing by C3H mammary tumor-bearing mice produced a 6-fold decrease in the 19FRI compared to air-breathing mice. The data presented support the preclin. and clin. development of SR-4554 as a noninvasive probe for tumor hypoxia.

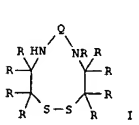
IT **167648-73-9**, SR-4554
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preclin. evaluation of the fluorinated 2-nitroimidazole SR-4554 as a probe for the measurement of tumor hypoxia)
RN 167648-73-9 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)- (9CI) (CA INDEX NAME)



L11 ANSWER 31 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:204309 CAPLUS
DOCUMENT NUMBER: 126:206814
TITLE: Heteroatom-bearing bridged amine oxime ligands and analogs and their metal complexes for use in diagnostic and therapeutic methods
INVENTOR(S): Ramalingam, Kondareddiar; Raju, Natarajan
PATENT ASSIGNEE(S): Bracco International B.V., Neth.
SOURCE: U.S., 38 pp., Cont.-in-part of U.S.Ser.No. 77981, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5608110	A	19970304	US 1994-242093	19940518
AT 165598	E	19980515	AT 1994-108968	19940610
ES 2115805	T3	19980701	ES 1994-108968	19940610
FI 9402795	A	19941216	FI 1994-2795	19940613
NO 9402231	A	19941216	NO 1994-2231	19940614
AU 9464672	A1	19941222	AU 1994-64672	19940614
AU 678001	B2	19970515		
ZA 9404201	A	19950208	ZA 1994-4201	19940614
CA 2125895	AA	19941216	CA 1994-2125895	19940615
CN 1099388	A	19950301	CN 1994-106661	19940615
CN 1055685	B	20000823		
JP 07089922	A2	19950404	JP 1994-133037	19940615
US 5627286	A	19970506	US 1995-472058	19950606
US 5656254	A	19970812	US 1995-471590	19950606
US 5665329	A	19970909	US 1995-480048	19950606
US 5741912	A	19980421	US 1995-479076	19950606
PRIORITY APPLN. INFO.:			US 1993-77981 B2	19930615
			US 1994-242093 A3	19940518

OTHER SOURCE(S): MARPAT 126:206814
GI



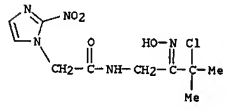
I

AB The invention provides for novel heteroatom-bearing bridged amine oxime ligands HON:CR*CRRNH-Q-NHCRRCR*:NOH, and the analogs disulfide-bridged cyclic compds. I and R1SCRRCRRNH-Q-NRCRRCRRSR1 [Q = -(C(RR))m1-Y1-(C(RR))m2-(Y2-C(RR)m3)n-, where Y1 and Y2 = NR, O, S, SO, SO2, Se; n = 0,

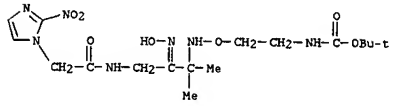
L11 ANSWER 31 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

1; m1, m2, m3 = 0-4 where m1 + m2 > 0; R and R* = R2, halo (esp. F), OR2, CO2R2, CON(R2)2, acyl, acyloxy, heterocyclo, hydroxyalkyl, etc., where a carbon atom bearing an R group is not directly bonded to more than one heteroatom; R1 = H, thiol protecting group, etc.; R2 = H, alkyl, alkenyl, alkynyl, aryl]. The invention provides for said amine oxime ligands above to contain a hypoxia-localizing moiety. The invention relates to complexes of these ligands, preferably with Re or Tc, which are useful in diagnostic and therapeutic methods. The invention relates further to kits for prepg. the metal complexes. In preferred embodiments, the invention relates to complexes of these ligands which contain bioactive moieties, e.g., hypoxia-localizing moieties, which are capable of rapidly increasing amts. of a desired radionucleotide selectively to targeted areas. In an example, reaction of 1-(2-aminoethyl)-1-methylhydrazine (prepn. given) and 3-chloro-3-methyl-2-nitrosobutane in the presence of iPr2NEt afforded HON:CMeCMe2NHCH2CH2NMeNHCMe2CMe:NOH in 26% yield. Reaction of this ligand in saline with eluate from a 99Mo/Tc generator, followed by addn. of tin tartrate in saline afforded oxo[(3,3,5,9,9-pentamethyl-4,5,8-triazaundecanedioximato)(3-)-N,N',N'',N''']technetium-99mTc(V) with >99% radiochem. purity (detd. after 5 min. at room temp.).

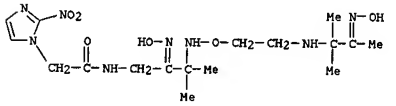
IT **161490-39-7P 161490-40-0P 161490-41-1P**
187847-72-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(prepn. of heteroatom-bearing bridged amine oxime ligands, analogs, and their metal complexes for use in diagnostic or therapeutic methods)
RN 161490-39-7 CAPLUS
CN 1H-Imidazole-1-acetamide, N-[3-chloro-2-(hydroxyimino)-3-methylbutyl]-2-nitro- (9CI) (CA INDEX NAME)



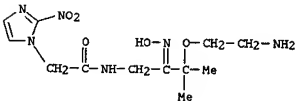
L11 ANSWER 31 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
RN 161490-40-0 CAPLUS
CN 5-Oxa-2,6,10-triazadodecanoic acid, 8-(hydroxyimino)-7,7-dimethyl-12-(2-nitro-1H-imidazol-1-yl)-11-oxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



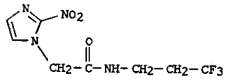
RN 161490-41-1 CAPLUS
CN 1H-Imidazole-1-acetamide, N-[2-(hydroxyimino)-3-[[2-[[2-(hydroxyimino)-1,1-dimethylpropyl]amino]ethoxy]amino]-3-methylbutyl]-2-nitro- (9CI) (CA INDEX NAME)



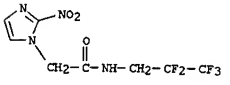
RN 187847-72-9 CAPLUS
CN 1H-Imidazole-1-acetamide, N-[3-(2-aminoethoxy)-2-(hydroxyimino)-3-methylbutyl]-2-nitro- (9CI) (CA INDEX NAME)



L11 ANSWER 32 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



IT 152721-37-4P
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hypoxia detection with 2-nitroimidazole compds. and immunogenic conjugates)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)



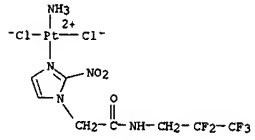
L11 ANSWER 32 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:494670 CAPLUS
DOCUMENT NUMBER: 125:162343
TITLE: Detection of hypoxia with reagents containing 2-nitroimidazole compounds and methods of making such reagents
INVENTOR(S): Koch, Cameron J.; Lord, Edith M.
PATENT ASSIGNEE(S): The Trustees of the Univ. of Pennsylvania, USA; The University of Rochester
SOURCE: U.S., 29 pp., Cont.-in-part of U.S. Ser. No. 978,918, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5540908	A	19960730	US 1994-286065	19940804
CA 2149770	AA	19940526	CA 1993-2149770	19931118
US 5843404	A	19981201	US 1996-598752	19960208
US 6252087	B1	20010626	US 1998-123300	19980728
PRIORITY APPLN. INFO.:			US 1992-978918 B2	19921119
			US 1994-286065 A3	19940804
			US 1996-598752 A2	19960208

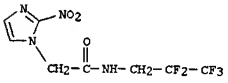
OTHER SOURCE(S): MARPAT 125:162343
AB Novel nitroarom. compds. and immunogenic conjugates comprising a novel nitroarom. compd. and a carrier protein are disclosed. The invention further presents monoclonal antibodies highly specific for the claimed nitroarom. compds., protein conjugates of the compds., reductive byproducts of the compds., and adducts formed between the compds. and mammalian hypoxic cell tissue proteins. The invention is further directed to methods for detecting tissue hypoxia using immunohistol. techniques, noninvasive nuclear medicine methods (PET, SPECT), or NMR. Diagnostic kits useful in practicing the methods of claimed invention are also provided.
IT 180208-73-5P
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(hypoxia detection with 2-nitroimidazole compds. and immunogenic conjugates)
RN 180208-73-5 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoropropyl)- (9CI) (CA INDEX NAME)

L11 ANSWER 33 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:492707 CAPLUS
DOCUMENT NUMBER: 125:185094
TITLE: Immunocytochemical labeling of aerobic and hypoxic mammalian cells using a platinated derivative of EF5
AUTHOR(S): Matthews, J.; Adomat, H.; Farrell, N.; King, P.; Koch, C.; Lord, E.; Palcic, B.; Poulin, N.; Sangulin, J.; Skov, K.
CORPORATE SOURCE: Department Medical Biophysics, BC Cancer Research Centre, Vancouver, BC, V5Z 1L3, Can.
SOURCE: British Journal of Cancer, Supplement (1996), 74(27), S200-S203
CODEN: BJCSB5; ISSN: 0306-9443
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The monoclonal antibody ELK3-51 was previously developed to detect adducts of the 2-nitroimidazole EF5. Direct immunofluorescence was used to detect adducts of EF5 or of a platinated deriv. cis-[PtCl2(NH3)EF5] in SCCVII cells treated under aerobic or hypoxic conditions. Fluorescence measurements of these cells using both image and flow cytometric methods were compared, giving similar profiles. Platination significantly decreased immunofluorescence levels (.apprx.4-fold less than EF5) after 3 h in hypoxia, but also increased levels after exposure in air (.apprx.1.5 .times.) such that the hypoxic ratio decreased from .apprx.50 to .apprx.13. Platinated EF5 also showed significantly greater cytotoxicity than its parent in both aerobic and hypoxic cells. These results are consistent with targeting of EF5 to DNA, which was confirmed qual. by confocal microscopy.
IT 180990-37-8
RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(immunocytochem. labeling of aerobic and hypoxic mammalian cells using a platinated deriv. of EF5)
RN 180990-37-8 CAPLUS
CN Platinum, amminedichloro[2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-1H-imidazole-1-acetamide-N3]-, (SP-4-3)- (9CI) (CA INDEX NAME)

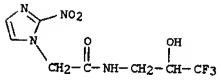
L11 ANSWER 33 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



IT **152721-37-4**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(immunocytochem. labeling of aerobic and hypoxic mammalian cells using
a platinated deriv. of EF5)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-(9CI)
(CA INDEX NAME)



L11 ANSWER 34 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
(Process)
(pharmacokinetics, bioavailability and biodistribution of tumor hypoxia
probe SR-4554)
RN 167648-73-9 CAPLUS
CN 1H-Imidazole-1-acetamide,
2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)-
(9CI) (CA INDEX NAME)

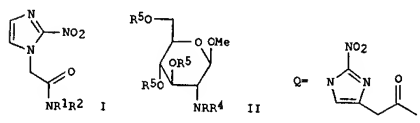


L11 ANSWER 34 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:427991 CAPLUS
DOCUMENT NUMBER: 125:131550
TITLE: The pharmacokinetics, bioavailability and biodistribution in mice of a rationally designed 2-nitroimidazole hypoxia probe SR-4554
AUTHOR(S): Aboagye, Eric O.; Lewis, Alexander D.; Graham, Martin
A.; Tracy, Mike; Kelson, Andrew B.; Ryan, Kenneth J.,
Workman, Paul
CORPORATE SOURCE: CRC Department of Medical Oncology, University of Glasgow, Glasgow, G61 1 BD, UK
SOURCE: Anti-Cancer Drug Design (1996), 11(3), 231-242
CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB N-(2-Hydroxy-3,3,3-trifluoropropyl)-2-(2-nitro-1-imidazolyl) acetamide (SR-4554) is a fluorinated 2-nitroimidazole which has been rationally designed as non-invasive probe for tumor hypoxia. The key selection criteria for this mol. were low central nervous system penetration and toxicity, high metabolic stability other than nitroredn., good tumor uptake and high sensitivity for detection by magnetic resonance spectroscopy. As part of the pre-clin. development strategy, pharmacokinetic, bioavailability and biodistribution studies were performed in mice. Pharmacokinetic studies in mice demonstrated that SR-4554 was rapidly absorbed into plasma following i.p. administration and eliminated with a half-life of 42 min, similar to other 2-nitroimidazoles. By comparing the areas under the concn.-time-curve (AUC), the tumor exposure towards SR-4554 was on av. 84% of the value obtained for the plasma exposure. SR-4554 penetrated tumor tissue extremely well but, in contrast to misonidazole and certain other fluorinated analogs, its distribution into brain tissue was poor (AUCbrain/AUCplasma = 0.07), suggesting potentially lower toxicity in spite of its higher lipophilicity (P = 0.43 vs. 0.63, resp.). The bioavailability of SR-4554 from i.p. and p.o. routes was 100 and 96% resp. In non-tumor-bearing mice, SR-4554 was excreted mainly as unchanged drug. The percentage of the injected p.p. dose of SR-4554 excreted unchanged in the urine over 24 h was 68 .+-. 8%. Neither SR-4554 nor its metabolites were detected in mouse feces. We propose that these favorable pharmacokinetic properties of SR-4554 are due to the hydrophilic character and hydrogen-bonding capability of the amide and hydroxyl functions in the compd.
IT **167648-73-9P**, SR-4554
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN
(Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC

L11 ANSWER 35 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:356969 CAPLUS
DOCUMENT NUMBER: 125:34039
TITLE: Preparation of fluorinated 2-nitroimidazole analogs for detecting hypoxic tumor cells
INVENTOR(S): Tracy, Michael; Kelson, Andrew B.; Workman, Paul; Lewis, Alexander D.; Aboagye, Eric O.
PATENT ASSIGNEE(S): Sri International, USA; University of Glasgow; Cancer Research Campaign Technology Limited
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9604249	A1	19960215	WO 1995-US9611	19950731
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5721265	A	19980224	US 1995-458178	19950602
EP 775117	A1	19970528	EP 1995-927535	19950731
EP 775117	B1	20011121		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 10506104	T2	19980616	JP 1995-506660	19950731
AT 209187	E	20011215	AT 1995-927535	19950731

PRIORITY APPLN. INFO.: US 1994-286477 A 19940805
US 1995-458178 A 19950602
WO 1995-US9611 W 19950731
OTHER SOURCE(S): MARPAT 125:34039
GI

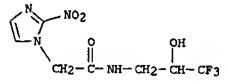


AB The title compds. [I; R1, R2 = H, monosaccharide (optionally functionalized to contain lower alkoxy, lower acyl, NH2, halo, or carboxylic acid moiety, wherein the linkage is to a carbon atom of the monosaccharide), lower alkyl substituted with CF3 and further substituted with at least one R3 (wherein R3 is selected from OH or optionally alkylated NH2), 5- or 6-membered heterocyclyl contg. one heteroatom selected from N, O, and S; or NR1R2 = 5- or 6-membered heterocyclyl contg. one heteroatom selected from N, O, and S (wherein if the heteroatom is N,

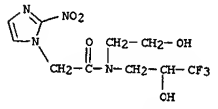
it may be substituted with lower alkyl or may be in halide or oxalate salt
form and further the 5- or 6-membered heterocyclic ring is substituted
with CF3 and optionally further substituted with OH, CH2OH, or NH2 on the
same C atom as the CF3); provided that at least one of R1 and R2 = lower
alkyl substituted with CF3 and further substituted with at least one R3
and that if either R1 or R2 contains .gtoreq.4 C atoms it is substituted
with .gtoreq.1 R3 groups] are prepd. These compds. I are useful for
detecting hypoxic tumor cells, wherein the detecting is carried out by
magnetic resonance imaging or magnetic resonance spectroscopy. Thus, Me
3,4,6-tri-O-acetyl-.beta.-D-glucosaminide (II; R = R4 = H, R5 = Ac)
(prepn. given) was alkylated with (trifluoromethyl)oxirane (prepn. given)
in MeCN at 85.degree. in a sealed tube to give II [R = CH2CH(OH)CF3, R4 =
H, R5 = Ac], which was condensed with 2-nitroimidazol-1-ylacetic acid
using iso-Bu chloroformate and N-methylmorpholine in THF and then treated
with NaOMe in MeOH to give the title compd. II [R = CH2CH(OH)CF3, R4 = Q,
R5 = H]. The title compd. I [R1 = H, R2 = CH2CH(OH)CF3] was injected at
180 mg/kg i.p. to RIF-tumor-bearing female C3H/He and magnetic resonance
spectroscopy (MRS) was conducted on a 4.7 T NMR using a double tuned
(19F/2H) circuit at 6 h and 45 min post injection of the drug. Tumors
were excised immediately after MRS examn. and the original drug levels
detd. by HPLC. The test results indicated that the drug was rapidly
cleared from brain but selectively retained in tumors.

IT **167648-73-9P 177595-17-4P 177595-18-5P**
177595-19-6P 177595-20-9P 177595-21-0P
177595-22-1P
RL: ARG (Analytical reagent use); BAC (Biological activity or effector,
except adverse); BSU (Biological study, unclassified); SPN (Synthetic
preparation); THU (Therapeutic use); ANST (Analytical study); BIOL
(Biological study); PREP (Preparation); USES (Uses)
(prepn. of fluorinated nitroimidazole analogs for detecting hypoxic
tumor cells by magnetic resonance imaging or NMR)

RN 167648-73-9 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)- (9CI) (CA INDEX NAME)

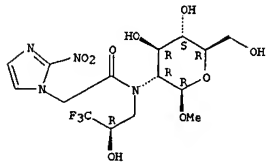


RN 177595-17-4 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2-hydroxyethyl)-2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)- (9CI) (CA INDEX NAME)



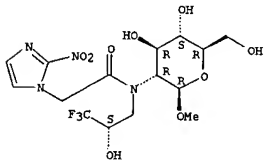
RN 177595-18-5 CAPLUS
CN .beta.-D-Glucopyranoside, methyl 2-deoxy-2-[[(2-nitro-1H-imidazol-1-yl)acetyl](3,3,3-trifluoro-2-hydroxypropyl)amino]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

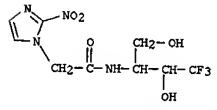


RN 177595-19-6 CAPLUS
CN .beta.-D-Glucopyranoside, methyl 2-deoxy-2-[[(2-nitro-1H-imidazol-1-yl)acetyl](3,3,3-trifluoro-2-hydroxypropyl)amino]-, (S)- (9CI) (CA INDEX NAME)

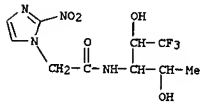
Absolute stereochemistry.



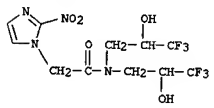
RN 177595-20-9 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-[3,3,3-trifluoro-2-hydroxy-1-(hydroxymethyl)propyl]- (9CI) (CA INDEX NAME)



RN 177595-21-0 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-[3,3,3-trifluoro-2-hydroxy-1-(1-hydroxyethyl)propyl]- (9CI) (CA INDEX NAME)



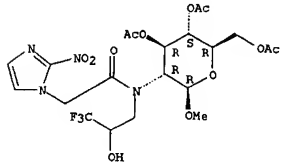
RN 177595-22-1 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N,N-bis(3,3,3-trifluoro-2-hydroxypropyl)- (9CI) (CA INDEX NAME)



IT **177595-25-4**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of fluorinated nitroimidazole analogs for detecting hypoxic tumor cells by magnetic resonance imaging or NMR)

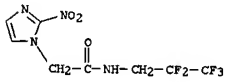
RN 177595-25-4 CAPLUS
CN .beta.-D-Glucopyranoside, methyl 2-deoxy-2-[[(2-nitro-1H-imidazol-1-yl)acetyl](3,3,3-trifluoro-2-hydroxypropyl)amino]-, 3,4,6-triacetate (9CI)
(CA INDEX NAME)

Absolute stereochemistry.



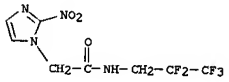
L11 ANSWER 36 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:293265 CAPLUS
DOCUMENT NUMBER: 125:4533
TITLE: Biodistribution of the nitroimidazole EF5 (2-[2-nitro-1H-imidazol-1-yl]-N-(2,2,3,3,3-pentafluoropropyl)acetamide) in mice bearing subcutaneous EMT6 tumors
AUTHOR(S): Laughlin, K. M.; Evans, S. M.; Jenkins, W. T.; Tracy, M.; Chan, C. Y.; Lord, E. M.; Koch, C. J.
CORPORATE SOURCE: Dep. Radn. Oncology, Univ. Pennsylvania, Philadelphia, PA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1996), 277(2), 1049-1057
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The characteristic redn. and binding of nitroimidazoles to cellular macromols. in the absence of oxygen allows their use for detection and characterization of hypoxia. The biodistribution of a new nitroimidazole, EF5 (2-[2-nitro-1H-imidazol-1-yl]-N-(2,2,3,3,3-pentafluoropropyl)acetamide), in mice bearing EMT6 tumors is described. Detection methods based on radioactivity and monoclonal antibody techniques are compared for liver and tumor. All nonexcretory tissues demonstrated similar levels of radioactivity at 0.5 h postinjection of drug, demonstrating equiv. access of EF5 to all tissues. At 24 h, when unbound drug has been cleared, the tissues with the highest binding are the liver, esophagus, bladder and tumor. Typically, liver tissue contains the highest level of radio-activity at this time. Examn. of tumor and liver tissue by use of fluorescence microscopy and Cy3-bound monoclonal antibodies specific for EF5 adducts showed the patterns of binding in tumor are considerably more heterogeneous than those of liver. Histograms of fluorescence intensity, with use of these antibodies, demonstrate av. and maximal binding higher in tumors than in the liver. This divergence from the radioactivity data was detd. to be unrelated to sampling error, differential antibody access or staining efficiency of liver vs. tumor tissue. A possible cause is the scavenging of radioactive drug metabolites by liver. The data presented herein suggest that EF5 is useful as a hypoxia detector and that monoclonal antibody detection

L11 ANSWER 36 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
methods can give detailed information on the distribution of EF5 binding. This technol. may allow an accurate estn. of the oxygenation and/or nitroreductase levels in both tumor and normal tissues.
IT **152721-37-4**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(biodistribution of nitroimidazole EF5 in tumor and liver and other tissues in relation to hypoxia detection)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-(9CI)
(CA INDEX NAME)



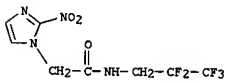
L11 ANSWER 37 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:60562 CAPLUS
DOCUMENT NUMBER: 124:139857
TITLE: 2-Nitroimidazole (EF5) binding predicts radiation resistance in individual 9L s.c. tumors
AUTHOR(S): Evans, Sydney M.; Jenkins, W. Timothy; Joiner, Barbara; Lord, Edith M.; Koch, Cameron J.
CORPORATE SOURCE: Sch. of Veterinary Medicine, Univ. of Pennsylvania, Pennsylvania, PA, 19104, USA
SOURCE: Cancer Research (1996), 56(2), 405-11
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The presence of hypoxic tumor cells cell is known to be an important cause of radiation treatment resistance in vivo. The ability to predict the presence and extent of hypoxic cells in individual tumors would allow the addn. of specific "antihypoxia"-based treatment regimes. Hypoxia can be monitored by measuring the binding of 2-nitroimidazoles. We have tested the hypothesis that binding of EF5, a fluorinated deriv. of the 2-nitroimidazole, Etanidazole, can predict radioresistance in individual tumors. Fischer rats bearing 9L s.c. tumors were given injections i.v. with EF5 3 h before irradn. and tumor harvest. Tumor cells were dissocd. for flow cytometric anal. and plating efficiency studies. EF5 binding was detected via monoclonal antibodies conjugated to the orange emitting dye, Cy3. In air breathing rats, for a given radiation dose, a large amt. of variation in plating efficiency was seen. However, there was minimal variability of the plating efficiency for tumors irradiated in euthanized animals (hypoxic tumors; correlation coeff. for the fitted curve = 0.93) and in cells dissocd. from tumors and irradiated in suspension (correlation coeff. for the fitted curve = 0.99), suggesting that varying sensitivity to the cell disaggregation technique was not responsible. In contrast, a good correlation between the relative radiation resistance or hypoxic survival and EF5 binding of "moderately" hypoxic cells in air breathing rats was identified using these techniques. In these 9L s.c. tumors, intertumor variation in oxygenation accounted for most of the range in individual tumor radiation response, and this was found to be independent of tumor size. This study provides evidence for the

L11 ANSWER 37 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
application of EF5 binding with monoclonal antibody detection as an in vivo predictive assay of individual tumor hypoxia and resultant therapy resistance.
IT **152721-37-4**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(2-nitroimidazole (EF5) binding to tumor hypoxic fractions predicts x-ray resistance in individual 9L s.c. tumors)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-(9CI)
(CA INDEX NAME)

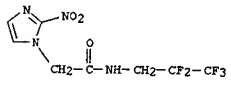


L11 ANSWER 38 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:1002637 CAPLUS
DOCUMENT NUMBER: 124:52283
TITLE: Mapping of the vascular endothelial growth factor-producing hypoxic cells in multicellular tumor spheroids using a hypoxia-specific marker
AUTHOR(S): Waleh, Nahid S.; Brody, Michael D.; Knapp, Merrill A.; Mendonca, Holly L.; Lord, Edith M.; Koch, Cameron J.; Laderoute, Keith R.; Sutherland, Robert M.
CORPORATE SOURCE: Cellular and Mol. Biol. Lab., Life Sci. Div., Menlo Park, CA, 94025, USA
SOURCE: Cancer Research (1995), 55(24), 6222-6
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have investigated the hypoxia inducibility of vascular endothelial growth factor (VEGF) in multicellular tumor spheroids of HT29 cells using a monoclonal antibody to a fluorinated bioreductive drug, EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide], a chem. probe for hypoxia. The authors have shown that VEGF expression is predominantly localized in interior spheroid cells that are sufficiently hypoxic to bioreductively activate the 2-nitroimidazole and produce immunol. detectable adducts of the EF5 compd. Northern blotting analyses demonstrated that VEGF165 is the predominant form of VEGF produced by HT29 cells and that the phorbol ester 12-O-tetradecanoylphorbol-13-acetate did not induce VEGF expression. This study demonstrates that VEGF expression is up-regulated in response to hypoxia and in the microenvironments found in human multicellular tumor spheroids. This investigation also illustrates the utility of the EF5 binding in multicellular tumor spheroids as a means of studying the expression and regulation of hypoxia-inducible genes.
IT **152721-37-4**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(vascular endothelial growth factor expression colocalization with EF5 binding in hypoxic regions of multicellular tumor spheroids of human HT29 cells)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-(9CI)

L11 ANSWER 38 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
(CA INDEX NAME)

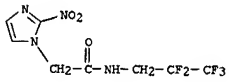


L11 ANSWER 39 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:936067 CAPLUS
DOCUMENT NUMBER: 124:44585
TITLE: Identification of hypoxia in cells and tissues of epigastric 9L rat glioma using EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide]
AUTHOR(S): Evans, S M.; Joiner, B.; Jenkins, W T.; Laughlin, K M.; Lord, E M.; Koch, C J.
CORPORATE SOURCE: Schools Veterinary Medicine (Clinical Studies), University Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: British Journal of Cancer (1995), 72(4), 875-82
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Macmillan Scientific & Medical Division
DOCUMENT TYPE: Journal
LANGUAGE: English
AB One of the most sensitive hypoxia detection methods is based on the observation that binding of nitroimidazoles to cellular macromols. occurs as a result of hypoxia-dependent bioredn. by cellular nitroreductases. Nitroimidazole-binding techniques provide measurements of hypoxia to virtually and degree of spatial resoln. and with a multiplicity of techniques. This paper demonstrates hypoxia imaging using in vivo EF5 binding with detection by a fluorochrome-conjugated monoclonal antibody. The authors investigated these techniques in the 9L glioma tumor, in part because the exact nature of the hypoxia in this tumor system is controversial. The results demonstrate that following i.v. injection of EF5, binding and detection using a monoclonal antibody in 9L gliomas is specific and oxygen dependent. Detection of binding using fluorescence microscopy can be performed on frozen tissues; tissue sections can be counterstained with haematoxylin and eosine for light microscopic anal. Alternatively, the distribution of hypoxia in a tumor can be inferred by examg. individual tumor cells using flow cytometric techniques. Based upon the results presented herein, the radiation-resistant phenotype of 9L epigastric tumors grown in the labs. can be assocd. with the presence of hypoxic cells.
IT **152721-37-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(identification of hypoxia in cells and tissues of epigastric 9L rat glioma using EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide])
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-(9CI)
(CA INDEX NAME)



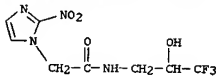
L11 ANSWER 40 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:936066 CAPLUS
DOCUMENT NUMBER: 124:44665
TITLE: Oxygen dependence of cellular uptake of EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide]: Analysis of drug adducts by fluorescent antibodies vs. bound radioactivity
AUTHOR(S): Koch, C. J.; Evans, S. M.; Lord, E. M.
CORPORATE SOURCE: Radiation Oncology, University Pennsylvania, Philadelphia, PA, 19104-6072, USA
SOURCE: British Journal of Cancer (1995), 72(4), 869-74
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Macmillan Scientific & Medical Division
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present studies were initiated to quantitate the oxygen dependence of bioreductive metab.-induced binding of EF5, a pentafluorinated deriv. of the 2-nitroimidazole, etanidazole. Two different assays were compared: first, radioactive drug incorporation into cell lysates, which provides a direct measure of drug metab. or uptake; second, monoclonal antibody detection of cellular macromol. adducts of EF5 after whole cell permeabilization and fixing. The antibodies (a single clone designated ELK3-51) were conjugated with the fluorescent dye Cy3, with fluorescence detd. by fluorescence microscopy and flow cytometry. For the two cell lines tested (V79 Chinese hamster fibroblasts and 9L rat glioma), the oxygen dependence of binding was the same for the two techniques. Using the antibody binding technique, the fluorescence signal was highly reproducible between expts., resistant to light or chem. bleaching and stable over time following cell or tissue staining. Flow cytometric anal. of cells from rat 9L tumors treated with EF5 in vivo or in vitro showed a distribution of fluorescent signal which was very compatible, on both a relative and abs. basis, with the in vitro results. The results indicate that immunofluorescent techniques provide a quant. assay for bioreductive drug adducts, and therefore may be able to measure the abs. oxygen concn. distribution in cell populations and tissues of interest.
IT **152721-37-4**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(oxygen dependence of cellular uptake of EF5 [2-(2-nitro-1H-imidazol-1-

L11 ANSWER 40 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide]: anal. of drug adducts by fluorescent antibodies vs. bound radioactivity)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-(9CI)
(CA INDEX NAME)



L11 ANSWER 41 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:865440 CAPLUS
DOCUMENT NUMBER: 123:309596
TITLE: Development and validation of a solid-phase extraction and high-performance liquid chromatographic assay for a novel fluorinated 2-nitroimidazole hypoxia probe (SR-4554) in Balb/c mouse plasma
AUTHOR(S): Aboagye, E. O.; Graham, M. A.; Lewis, A. D.; Workman, P.; Kelson, A. B.; Tracy, M.
CORPORATE SOURCE: Clinical Pharmacology and New Drug Development Team, CRC Department of Medical Oncology, University of Glasgow, CRC Beatson Laboratories, Alexander Stone Building, Garscube Estate, Switchback Road, Glasgow, G61 1BD, UK
SOURCE: Journal of Chromatography, B: Biomedical Applications (1995), 672(1), 125-32
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB N-(2-Hydroxy-3,3,3-trifluoropropyl)-2-(2-nitro-1-imidazolyl)acetamide, a novel 2-nitroimidazole, is currently being developed as a noninvasive probe for tumor hypoxia. A sensitive (min. quantifiable level = 25 ng/mL; C.V. = 6.01%) and selective assay has, therefore, been developed for the anal. of this compd. in mouse plasma. The assay employed solid-phase extn. followed by a rapid (10 min) HPLC anal. with UV-photodiode-array detection. No drug-related metabolites were obsd. in plasma when mice were treated with 180 mg/kg of the drug. The assay was suitable for studying the plasma pharmacokinetics of this fluorinated 2-nitroimidazole in mice.
IT **167648-73-9**, SR 4554
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(extn. and HPLC assay of fluorinated 2-nitroimidazole hypoxia probe (SR-4554) in Balb/c mouse plasma)
RN 167648-73-9 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)-(9CI) (CA INDEX NAME)

L11 ANSWER 41 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

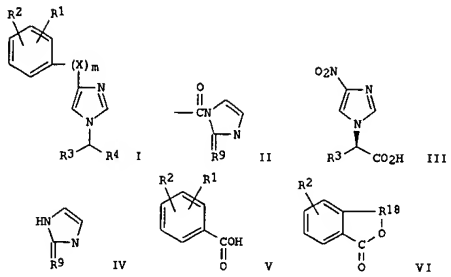


L11 ANSWER 42 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:835486 CAPLUS
DOCUMENT NUMBER: 123:257395
TITLE: Imidazolyl amino acid derivatives as angiotensin II antagonists
INVENTOR(S): Boyd, Donald B.; Hauser, Kenneth L.; Lifer, Sherryl L.; Marshall, Winston S.; Palkowitz, Alan D.; Pfeifer, William; Reel, Jon K.; Simon, Richard L.; Steinberg, Mitchell I.; et al.
PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA
SOURCE: U.S., 29 pp. Cont.-in-part of U.S. Ser. No. 892,867, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5401851	A	19950328	US 1993-49917	19930420
CA 2097462	AA	19931204	CA 1993-2097462	19930601
HU 64328	A2	19931228	HU 1993-1603	19930601
IL 105877	A1	19980715	IL 1993-105877	19930601
NO 9302005	A	19931206	NO 1993-2005	19930602
EP 573271	A1	19931208	EP 1993-304264	19930602
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AU 9339985	A1	19940120	AU 1993-39985	19930602
AU 667903	B2	19960418		
RU 2110515	C1	19980510	RU 1993-46497	19930602
CN 1085897	A	19940427	CN 1993-107578	19930603
CN 1045768	B	19991020		
JP 07304752	A2	19951121	JP 1993-133212	19930603
PL 173340	B1	19980227	PL 1993-299176	19930603
US 5484780	A	19960116	US 1994-355778	19941214

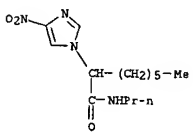
PRIORITY APPLN. INFO.: US 1992-892867 B2 19920603
US 1993-49917 A 19930420
OTHER SOURCE(S): MARPAT 123:257395
GI

L11 ANSWER 42 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



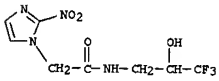
AB A process of prepg. a substantially pure (R) enantiomer of the compd. of the formula I wherein: R1 is CO2H, SO3H, PO3H2, CONHSO2R5 or 5-tetrazolyl; R2 is H, OH, OCOCH3, halo, C1-C4 alkyl, amino, acetamido, or C1-C4 alkoxy; X is (CH2)mNHCO, (CH2)mCONH, O, NH, CH2, (CH2)mCO, or CO(CH2)m ; R3 is C4-C9 straight chain alkyl, C4-C9 straight chain trifluoroalkyl, C4-C9 straight chain alkenyl, or C4-C9 straight chain trifluoroalkenyl; R4 is CONH(C1-C4 alkyl), CONH(C1-C4 trifluoroalkyl), CONH(hydroxy-C1-C4 alkyl), or, e.g., II; R5 is Ph, C1-C4 alkyl substituted Ph, C1-C5 alkyl, or C1-C5 trifluoroalkyl; R9 is O or S; m is independently 0 or 1; p is independently 0, 1, 2, 3 or 4; and q is 1, 2, 3, or 4 (with provisos); comprising coupling a compd. of the formula III to, e.g., IV; reducing the nitro of the compd. of the formula III to produce an aminoimidazole; coupling the aminoimidazole to V or VI (R18 = SO2 or CO). Thus, e.g., reaction of 4-nitroimidazole with Et 2-bromooctanoate afforded Et 2-(4-nitro-1H-imidazol-1-yl)octanoate; reaction of the latter with ethylamine afforded N-ethyl-2-(4-nitro-1H-imidazol-1-yl)octanoamide; N-ethyl-2-(4-nitro-1H-imidazol-1-yl)octanoamide was reduced by hydrogenation at 40 psi over Pd/C and the aminoimidazole was added to a soln. of 2-sulfobenzoic acid cyclic anhydride to afford N-ethyl-2-[4-(2-sulfobenzoyl)amino-1H-imidazol-1-yl]octanoamide (VII). The ability of I to block angiotensin II receptor binding (KI, .mu.M) was detd. using the adrenal glomerulosa assay, and the ability to antagonize angiotensin-induced vasoconstriction [potency = pA2 (defined as -log KB,

L11 ANSWER 42 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
where KB = [molar concn. of antagonist]/[(EC50 AII with antagonist/EC50 AII without antagonist)-1])] was evaluated in the rabbit aorta test system: for VII, KI = 10.3 and pA2 = 5.7. Pharmaceutical formulations were given.
IT **157187-22-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(imidazolyl amino acid derivs. as angiotensin II antagonists)
RN 157187-22-9 CAPLUS
CN 1H-Imidazole-1-acetamide, .alpha.-hexyl-4-nitro-N-propyl- (9CI) (CA INDEX NAME)



L11 ANSWER 43 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:750169 CAPLUS
DOCUMENT NUMBER: 123:192723
TITLE: The novel fluorinated 2-nitroimidazole hypoxia probe SR-4554: reductive metabolism and semiquantitative localization in human ovarian cancer multicellular spheroids as measured by electron energy loss spectroscopy analysis
AUTHOR(S): Aboagye, EO; Lewis, AD; Johnson, A.; Workman, P.; Tracy, M.; Huxham, I. M.
CORPORATE SOURCE: CRC Dep. of Medical Oncology, Univ. of Glasgow, Glasgow, G61 1BD, UK
SOURCE: British Journal of Cancer (1995), 72(2), 312-18
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Macmillan Scientific & Medical Division
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The novel fluorinated 2-nitroimidazole SR-4554 is undergoing preclin. development as a magnetic resonance spectroscopy and imaging probe for hypoxic tumor cells. We have used electron energy loss spectroscopic anal. (EELS) to show selective redn. and differential subcellular localization of SR-4554 in human ovarian multicellular spheroids. SR-4554 was demonstrated to be metabolized by these A2780 cells under hypoxic but not under normal aerobic cell culture conditions. The EELS technique illustrated that the relative amt. of drug within the cytoplasm of cells from both the inner region (150-160 .mu.m from edge) and outer edge of the spheroid did not differ significantly after an initial 3 h incubation with drug. In contrast, an 8-fold differential between the amt. of drug retained in the cytoplasm (primarily ribosomes and endoplasmic reticulum) of cells from the inner vs outer regions of the spheroids was obsd. following a subsequent 2 h 'chase' culture in drug-free medium. Within cells from the hypoxic region of the spheroid, SR-4554 was mainly assocd. with the endoplasmic reticulum, nucleus and the cytoplasmic side of intracellular vesicles and also to a lesser extent with the nuclear periphery. Interestingly, the drug was only weakly assocd. with the mitochondria and plasma membrane of the cells. The characteristics of cellular and subcellular distribution of SR-4554 are consistent with the hypothesis that 2-nitroimidazole compds. undergo hypoxia-mediated enzymic redn. to reactive species. These reactive species are selectively retained in the cells in which they are metabolized through covalent assocn. with subcellular components. These findings provide addnl. support for the clin. development of the drug as a non-invasive probe for tumor hypoxia and at the same time illustrate the utility of the EELs technique for examg. the heterogenicity of drug distribution both between

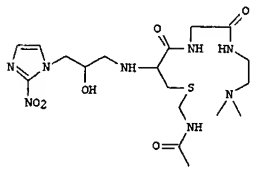
L11 ANSWER 43 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
and within cells.
IT **167648-73-9**, SR 4554
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(the fluorinated 2-nitroimidazole hypoxia probe SR-4554 and reductive
metab. and semiquant. localization in human ovarian cancer multicellular spheroids as measured by electron energy loss spectroscopy anal.)
RN 167648-73-9 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)- (9CI) (CA INDEX NAME)



L11 ANSWER 44 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:638235 CAPLUS
DOCUMENT NUMBER: 123:83362
TITLE: Preparation of metal chelating compounds.
INVENTOR(S): Archer, Colin Mill; Bower, Robert Gary; Gill, Harjit
Kaur; Riley, Anthony Leonard Mark; Storey, Anthony Eamon; Canning, Lewis Reuben; Griffiths, David Vaughan
PATENT ASSIGNEE(S): Amersham International PLC, UK
SOURCE: Eur. Pat. Appl., 45 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 618191	A1	19941005	EP 1993-302634	19930402
R: BE, DE, ES, FR, GB, IT, NL, SE				
WO 9422816	A1	19941013	WO 1994-GB693	19940331
W: AU, CA, JP, US				
CA 2136970	AA	19941013	CA 1994-2136970	19940331
AU 9463822	A1	19941024	AU 1994-63822	19940331
AU 672894	B2	19961017		
JP 07507331	T2	19950810	JP 1994-521844	19940331
JP 2860166	B2	19990224		
US 5932707	A	19990803	US 1997-888398	19970707
US 6004531	A	19991221	US 1997-917476	19970826

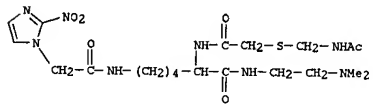
PRIORITY APPLN. INFO.: EP 1993-302634 19930402
WO 1994-GB693 19940331
US 1997-888398 19970707
OTHER SOURCE(S): MARPAT 123:83362
GI



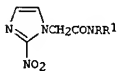
I

AB Ligands A(CR2)nB(CR2)mRN(CR2)nA', ZS(CR2)mXN(CR2)nXN(CR2)mY (A, A' = ZS, Y; B = O, S wherein Y = R(CR2)qNR, Z = H, thiol protectant; m, n = 2,3, q= 0,1,; R = H, C1-20 alkyl, or alkenyl, or alkoxy, or alkoxyalkyl, amide,

L11 ANSWER 44 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
amine, HO2C, HO-alkyl, aryl, or 2 R's of any R2C and/or 2 or more adjacent
R2C may by combined to form C3-6 cycloalkyl, aryl, heteroaryl, etc.; X =
R) and a salt thereof, are prep. The ligands and their resp. radiometal
complexes can be bound to biol. targeting mols. 1-(2,3-Epoxypropyl)-2-
nitroimidazole in MeOH was to AcNHCH2SCH2CH(NH2)CONHCH2CONH(CH2)2NMe2
(prepn. given) in MeOH to give the title ligand (I). I was labeled with
99mTc and the hypoxic and oxic binding to cells in vitro shown.
IT **164213-58-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of metal chelating compds.)
RN 164213-58-5 CAPLUS
CN 1H-Imidazole-1-acetamide, N-[5-[[[[(acetylamino)methyl]thio]acetyl]amino]-6-[[2-(dimethylamino)ethyl]amino]-6-oxohexyl]-2-nitro- (9CI) (CA INDEX NAME)

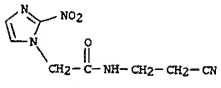


L11 ANSWER 45 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:525695 CAPLUS
DOCUMENT NUMBER: 123:313839
TITLE: Synthesis and polyamine derivatives of 2-nitroimidazole as DNA-directed radiosensitizers
AUTHOR(S): Parrick, John; Porssa, Manuchehr
CORPORATE SOURCE: Dep. Chem., Brunel Univ., Uxbridge, UB8 3PH, UK
SOURCE: Journal of Chemical Research, Synopses (1995), (5), 186-7
CODEN: JRPSDC; ISSN: 0308-2342
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



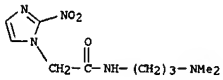
I

AB The synthesis of a series of 1-substituted amino derivs. of 2-nitroimidazole, via an improved route to N-(aminoalkyl)-2-nitroimidazol-1-ylacetamides I (R, R1 = H, aminoalkyl) was described. The pharmacol. activity of I was not reported here.
IT **165062-76-0P 165062-77-1P 165062-78-2P**
165062-79-3P 165062-80-6P 165062-82-8P
165062-83-9P 165062-84-0P 165062-85-1P
165062-86-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
((aminoalkyl)nitro-1H-imidazoleacetamides DNA-directed radiosensitizers)
RN 165062-76-0 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2-cyanoethyl)-2-nitro- (9CI) (CA INDEX NAME)

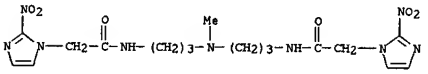


RN 165062-77-1 CAPLUS
CN 1H-Imidazole-1-acetamide, N-[3-(dimethylamino)propyl]-2-nitro- (9CI) (CA INDEX NAME)

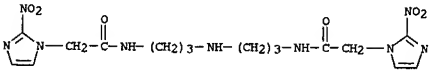
L11 ANSWER 45 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



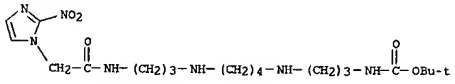
RN 165062-78-2 CAPLUS
CN 1H-Imidazole-1-acetamide,
N,N'-[(methylimino)di-3,1-propanediyl]bis[2-
nitro- (9CI) (CA INDEX NAME)



RN 165062-79-3 CAPLUS
CN 1H-Imidazole-1-acetamide, N,N'-(iminodi-3,1-propanediyl)bis[2-nitro-
(9CI)
(CA INDEX NAME)



RN 165062-80-6 CAPLUS
CN 2,6,11,15-Tetraazaheptadecanoic acid,
17-(2-nitro-1H-imidazol-1-yl)-16-oxo-
, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

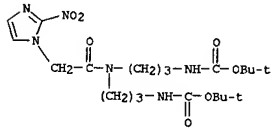


RN 165062-82-8 CAPLUS
CN 1H-Imidazole-1-acetamide,
N-[3-[[4-[(3-aminopropyl)amino]butyl]amino]propy
l]-2-nitro-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

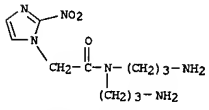
CM 1

CRN 165062-81-7
CMF C15 H29 N7 O3

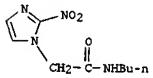
L11 ANSWER 45 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
NAME)



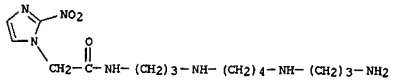
RN 165062-86-2 CAPLUS
CN 1H-Imidazole-1-acetamide, N,N-bis(3-aminopropyl)-2-nitro- (9CI) (CA
INDEX
NAME)



IT **22668-00-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
((aminoalkyl)nitro-1H-imidazoleacetamides DNA-directed
radiosensitizers)
RN 22668-00-4 CAPLUS
CN 1H-Imidazole-1-acetamide, N-butyl-2-nitro- (9CI) (CA INDEX NAME)



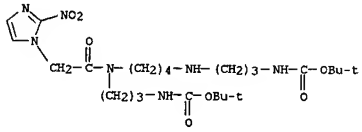
L11 ANSWER 45 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



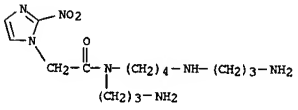
CM 2

CRN 76-05-1
CMF C2 H F3 O2

RN 165062-83-9 CAPLUS
CN 2,6,11,15-Tetraazahexadecanedioic acid, 6-[(2-nitro-1H-imidazol-1-
yl)acetyl]-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)



RN 165062-84-0 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-aminopropyl)-N-[4-[(3-
aminopropyl)amino]butyl]-2-nitro- (9CI) (CA INDEX NAME)



RN 165062-85-1 CAPLUS
CN 12-Oxa-2,6,10-triazatetradecanoic acid, 13,13-dimethyl-6-[(2-nitro-1H-
imidazol-1-yl)acetyl]-11-oxo-, 1,1-dimethylethyl ester (9CI) (CA
INDEX

L11 ANSWER 46 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:410624 CAPLUS
DOCUMENT NUMBER: 122:229386
TITLE: Heteroatom-bearing ligands and metal complexes thereof.
INVENTOR(S): Ramalingam, Kondareddiar; Raju, Natarajan
PATENT ASSIGNEE(S): Bristol-Myers Squibb So., USA
SOURCE: Eur. Pat. Appl., 76 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

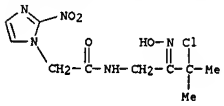
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 629617	A1	19941221	EP 1994-108968	19940610
EP 629617	B1	19980429		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 165598	E	19980515	AT 1994-108968	19940610
ES 2115805	T3	19980701	ES 1994-108968	19940610
FI 9402795	A	19941216	FI 1994-2795	19940613
NO 9402231	A	19941216	NO 1994-2231	19940614
AU 9464672	A1	19941222	AU 1994-64672	19940614
AU 678001	B2	19970515		
ZA 9404201	A	19950208	ZA 1994-4201	19940614
CA 2125895	AA	19941216	CA 1994-2125895	19940615
CN 1099388	A	19950301	CN 1994-106661	19940615
CN 1055685	B	20000823		
JP 07089922	A2	19950404	JP 1994-133037	19940615

PRIORITY APPLN. INFO.: US 1993-77981 A 19930615
OTHER SOURCE(S): MARPAT 122:229386
GI

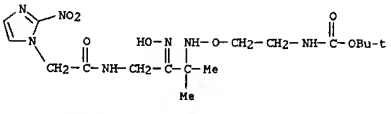
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Novel compds. contg. a heteroatom-bearing bridge (I, II, and III) and novel complexes of these compds. with metals are claimed. Details are given for the prepn. of dioxime ligands (I, Q = MeNCH2CH2, OCH2CH2, OCHRCH2) and their 99mTc complexes. The novel compds. and complexes are
useful as diagnostics and therapeutics.
IT **161490-39-7P 161490-40-0P 161490-41-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(for prepn. of technetium triaza or oxadiaza dioxime complexes)
RN 161490-39-7 CAPLUS
CN 1H-Imidazole-1-acetamide,
N-[3-chloro-2-(hydroxyimino)-3-methylbutyl]-2-
nitro- (9CI) (CA INDEX NAME)

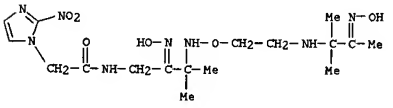
L11 ANSWER 46 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 161490-40-0 CAPLUS
CN 5-Oxa-2,6,10-triazadodecanoic acid, 8-(hydroxyimino)-7,7-dimethyl-12-(2-nitro-1H-imidazol-1-yl)-11-oxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 161490-41-1 CAPLUS
CN 1H-Imidazole-1-acetamide, N-[2-(hydroxyimino)-3-[[2-[[2-(hydroxyimino)-1,1-dimethylpropyl]amino]ethoxy]amino]-3-methylbutyl]-2-nitro- (9CI) (CA INDEX NAME)

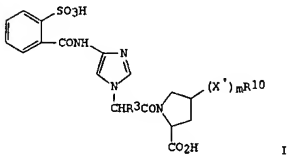


L11 ANSWER 47 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:558192 CAPLUS
DOCUMENT NUMBER: 121:158192
TITLE: Preparation of heterocyclyl-substituted L-proline as angiotensin II antagonists
INVENTOR(S): Boyd, Donald Bradford; Hauser, Kenneth Lee; Lifer, Sherryl Lynn; Marshall, Winston Stanley; Palkowitz, Alan David; Pfeifer, William; Reel, Jon Kevin; Simon, Richard Lee; Steinberg, Mitchell Irvin; et al.
PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA
SOURCE: Eur. Pat. Appl., 56 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 573271	A1	19931208	EP 1993-304264	19930602
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
US 5401851	A	19950328	US 1993-49917	19930420
PRIORITY APPLN. INFO.:			US 1992-892867 A	19920603
			US 1993-49917 A	19930420
OTHER SOURCE(S):		MARPAT 121:158192		

GI



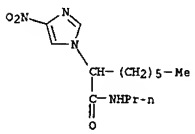
AB Title compds. I [R3 = C4-9 alkyl; R10 = p-(substituted) Ph, (substituted) fused bicyclyl or fused tricyclyl; m = 0,1; X' = O, S (CH2)p wherein p = 0-4] or a salt thereof, are prepd. (Me2CH)2NEt was added to D-proline benzyl ester-HCl in DMF followed by 2-(4-nitro-1H-imidazol-1-yl)octanoic acid to give a mixt of isomer esters which were reduced in EtOH with Pd/C, the catalyst filtered and to the product amine in THF was added sulfobenzoic anhydride to give D-I [R3 = C6H13, (X')mR10 is nill] as 2 isomers (II). The ability to antagonize angiotensin-induced

L11 ANSWER 47 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

vasoconstriction was evaluated in rabbit aorta test system where the pA2 of II was 6.6 and 6.7. A no. of imidazolyl derivs. were also prepd. and evaluated. Pharmaceutical formulation of I are given.

IT **157187-22-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction of, in prepn. of angiotensin II antagonists)

RN 157187-22-9 CAPLUS
CN 1H-Imidazole-1-acetamide, .alpha.-hexyl-4-nitro-N-propyl- (9CI) (CA INDEX NAME)



L11 ANSWER 48 OF 62 CAPLUS COPYRIGHT 2003 ACS

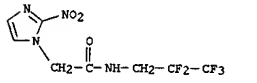
ACCESSION NUMBER: 1994:506516 CAPLUS
DOCUMENT NUMBER: 121:106516
TITLE: Monoclonal antibody to nitroaromatic compound for hypoxia detection
INVENTOR(S): Koch, Cameron J.; Lord, Edith M.
PATENT ASSIGNEE(S): University of Pennsylvania, USA; University of Rochester
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9411348	A1	19940526	WO 1993-US11190	19931118
W: CA, JP, LV, UZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2149770	AA	19940526	CA 1993-2149770	19931118
EP 669913	A1	19950906	EP 1994-902291	19931118
R: BE, CH, DE, DK, FR, GB, IT, LI				
JP 08503469	T2	19960416	JP 1993-512489	19931118
PRIORITY APPLN. INFO.:			US 1992-978918 A	19921119
			WO 1993-US11190 W	19931118
OTHER SOURCE(S):		MARPAT 121:106516		

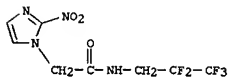
AB Novel nitroarom. compds. and immunogenic conjugates comprising a novel nitroarom. compd. and a carrier protein are disclosed. The invention further presents monoclonal antibodies highly specific for the claimed nitroarom. compds., the compds.' protein conjugates, the compds.' reductive byproducts, and adducts formed between the compds. and mammalian hypoxic cell tissue proteins. The invention is further directed to methods for detecting tissue hypoxia using immunohistol. techniques, non-invasive nuclear medicinal methods, or NMR. Diagnostic kits useful in practicing the methods of claimed invention are also provided.

IT **152721-37-4DP**, conjugates with albumin or lysozyme or Bowman-Birk inhibitor
RL: PREP (Preparation)
(prepn. of, as immunogen, for raising monoclonal antibody, for hypoxia detn.)

RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
(CA INDEX NAME)

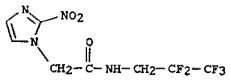


L11 ANSWER 48 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
IT **152721-37-4P**
RL: PREP (Preparation)
(prepn. of, for prepg. immunogen for raising monoclonal antibody for
hypoxia detn.)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-(9CI)
(CA INDEX NAME)

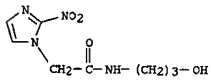


L11 ANSWER 49 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:101090 CAPLUS
DOCUMENT NUMBER: 120:101090
TITLE: Detection of hypoxic cells by monoclonal antibody recognizing 2-nitroimidazole adducts
AUTHOR(S): Lord, Edith M.; Harwell, Lee; Koch, Cameron J.
CORPORATE SOURCE: Cancer Cent., Univ. Rochester, Rochester, NY, 14642, USA
SOURCE: Cancer Research (1993), 53(23), 5721-6
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A pentafluorinated deriv. [EF5; 2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide] of etanidazole was synthesized with the expectation of lessening some of the non-oxygen-dependent variability in adduct formation obsd. previously with other nitroarom. compds. EF5-protein conjugates, prepd. by radiochem. redn., were found to be immunogenic and allowed the development of monoclonal antibodies. One of these antibodies, ELK2-4, has been characterized and found to be highly specific for the EF5 adducts whether produced radiochem. or by cellular bioreductive metab. The 9L rat glioma cells pretreated with EF5 under hypoxic, compared with aerobic, conditions were readily discriminated immunochem. using fluorochrome-conjugated secondary antibodies which recognize the ELK2-4 antibody subtype (IgG1). Similarly, the central region of multicellular spheroids, composed of EMT6 mouse mammary sarcoma cells, was selectively visualized by immunohistochem. after the spheroids were incubated for 4 h in 0.5 mM EF5. Tumor biopsy, prepn., and immunohistochem. staining 24 h after treatment of tumor-bearing animals with drug also demonstrated high contrast regions within EMT6 mouse or Morris 7777 hepatoma rat tumors. The use of this new compd. and its highly specific monoclonal antibody may allow elucidation of bioreductive metab. of the nitroheterocyclics and significantly improve technologies for the quantitation of tissue pO2.
IT **152721-37-4**
RL: ANST (Analytical study)
(in hypoxic cell detection with monoclonal antibodies)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-(9CI)
(CA INDEX NAME)

L11 ANSWER 49 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

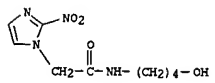


L11 ANSWER 50 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:608058 CAPLUS
DOCUMENT NUMBER: 117:208058
TITLE: Pharmacokinetics of fluorinated 2-nitroimidazole hypoxic cell radiosensitizers in murine peripheral nervous tissue
AUTHOR(S): Sasai, K.; Iwai, H.; Yoshizawa, T.; Nishimoto, S.; Shibamoto, Y.; Kitakabu, Y.; Oya, N.; Takahashi, M.; Abe, M.
CORPORATE SOURCE: Fac. Med., Kyoto Univ., Kyoto, 606, Japan
SOURCE: International Journal of Radiation Biology (1992), 62(2), 221-7
CODEN: IJRBE7; ISSN: 0955-3002
DOCUMENT TYPE: Journal
LANGUAGE: English
AB KU-2285, a 2-nitroimidazole with a fluorinated N1-substituent (-CH2CF2CONH(CH2)nOH, n = 2), has been shown to be a promising hypoxic cell radiosensitizer. In this study, the pharmacokinetics of KU-2285 and its related compds. (n = 3 and n = 4) were compared with those of etanidazole [a 2-nitroimidazole with an N1-substituent of -CH2CONH(CH2)nOH, n = 2] and its related compds. (n = 3 and n = 4) to assess the effects of incorporation of a CF2 group. The lipophilicity of the fluorinated compds. was higher than that of etanidazole, as measured by the octanol/water partition coeff. As the no. of CH2 groups increased, the lipophilicity of the compds. in both the KU-2285 and etanidazole series increased. The brain tissue levels of the fluorinated compds. were as low as those of the etanidazole derivs., while the biol. half-lives of the fluorinated compds. in peripheral nervous tissues were shorter than those of related nonfluorinated compds.
IT **144315-38-8**, KU 3205 **144315-39-9**, KU 3206
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pharmacokinetics of, as radiosensitizer, structure in relation to)
RN 144315-38-8 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-hydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)



RN 144315-39-9 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(4-hydroxybutyl)-2-nitro- (9CI) (CA INDEX

L11 ANSWER 50 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
NAME)



L11 ANSWER 51 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:6504 CAPLUS
DOCUMENT NUMBER: 114:6504
TITLE: Preparation of 3-(2-nitroimidazolo)-2,2-difluoropropionamides and analogs as radiosensitizers
INVENTOR(S): Kagiya, Tsutomu; Abe, Mitsuyuki; Nishimoto, Seiichi; Shibamoto, Yuta; Otomo, Susumu; Tanami, Tohru; Shimokawa, Kazuhiro; Yoshizawa, Toru; Hisanaga, Yorisato
PATENT ASSIGNEE(S): Nishijima, Yasunori, Japan; Taisho Pharmaceutical Co., Ltd.; Daikin Industries, Ltd.
SOURCE: Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

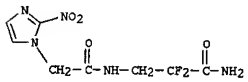
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 373630	A1	19900620	EP 1989-123062	19891213
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 2005261	AA	19900614	CA 1989-2005261	19891212
US 4977273	A	19901211	US 1989-448909	19891212
AU 8946713	A1	19900621	AU 1989-46713	19891213
AU 625581	B2	19920716		
ZA 8909503	A	19900926	ZA 1989-9503	19891213
JP 02275863	A2	19901109	JP 1989-325437	19891214

PRIORITY APPLN. INFO.: JP 1988-315974 19881214
OTHER SOURCE(S): CASREACT 114:6504; MARPAT 114:6504
GI

I

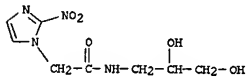
AB The title compds. [I; R = CH2CFXCH2OR1; R1 = CH2CH(OR2)CH2OR2, (CH2)1OR2, (CH2)1COR2, (CH2)m(CF2)n[CONH(CHR3)r(CF2)p]qZ, etc.; R2 = H, OH (sic), alkyl, acyl; R22 = PhCH, Me2C; R3 = H, alkyl; X = H, halo; Z = H, CO2R3, CO2H, CONH2, etc.; l = 1-3; m, n = 0-4; p = 0-2; q, r = 0-3] were prepd. as hypoxic cell sensitizers. Thus, I (R = CH2CF2CO2Me) was stirred 1 h with H2NCH2CH2CO2Me.HCl in MeOH contg. KOH and the product stirred 2 days with aq. NH3-MeOH contg. KOH to give I (R = CH2CF2CONHCH2CH2CONH2) which gave cell-survival rate of EMT-6 tumor cells X-irradiated in mouse thigh

L11 ANSWER 51 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
66% that of unirradiated cells after administration of 100 mg/kg i.p.
IT **130777-35-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as radiosensitizer)
RN 130777-35-4 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-amino-2,2-difluoro-3-oxopropyl)-2-nitro- (9CI) (CA INDEX NAME)



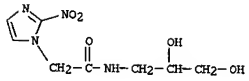
L11 ANSWER 52 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:449656 CAPLUS
DOCUMENT NUMBER: 99:49656
TITLE: Influence of heat on the intracellular uptake and radiosensitization of 2-nitroimidazole hypoxic cell sensitizers in vitro
AUTHOR(S): Brown, Dennis M.; Cohen, Mark S.; Sagerman, Robert H.; Gonzalez-Mendez, Ricardo; Hahn, George M.; Brown, J. Martin
CORPORATE SOURCE: Sch. Med., Stanford Univ., Stanford, CA, 94305, USA
SOURCE: Cancer Research (1983), 43(7), 3138-42
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of elevated temp. (44.degree.) on the intracellular uptake of the 2-nitroimidazole hypoxic cell radiosensitizer, misonidazole (MIS), and analogs more hydrophilic than MIS was studied in Chinese hamster ovary cells. The intracellular uptake of these compds., which enter cells by restricted passive diffusion, can be enhanced .apprx.4-fold when incubated at 44.degree. compared to the uptake at 37.degree.. Peak intracellular uptake (expressed as the ratio of intracellular concn. to extracellular concn.) following incubation of cells in 2 mM MIS was 100% at 44.degree. but only 25% at 37.degree.. Furthermore, a short-term nonlethal heat pulse (44.degree. for 15 min) with MIS present caused a 2-fold enhancement in uptake which was sustained for an addnl. 45 min at 37.degree.. This same nonlethal heat pulse induced a similar enhancement in uptake even when MIS was added at subsequent time intervals at 37.degree.. The heat pulse induced a time-related enhancement of uptake at 37.degree. which increased for 1 h and persisted for at least 6 h. Finally, in vitro radiosensitization studies of hypoxic Chinese hamster ovary cells showed that the nonlethal heat pulse of 44.degree. for 15 min could greatly enhance the sensitization by low concns. (0.5 mM) of MIS added after heating due to increased intracellular concns. of the drug. MIS (0.5 mM) alone achieved a radiosensitization enhancement ratio of 1.29 (compared to irradiated hypoxic cells alone), whereas the addn. of the short-term heat pulse, which had only a minor effect itself, achieved an enhancement ratio of 1.78.
IT **74141-75-6**

L11 ANSWER 52 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
RL: BIOL (Biological study)
(metab. of and radiosensitization by, of CHO cells, heat effect on)
RN 74141-75-6 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)



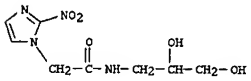
L11 ANSWER 53 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:122128 CAPLUS
DOCUMENT NUMBER: 98:122128
TITLE: Factors influencing intracellular uptake and radiosensitization by 2-nitroimidazoles in vitro
AUTHOR(S): Brown, Dennis M.; Gonzalez-Mendez, Ricardo; Brown, J. Martin
CORPORATE SOURCE: Sch. Med., Stanford Univ., Stanford, CA, 94305, USA
SOURCE: Radiation Research (1983), 93(3), 492-505
CODEN: RARAAE; ISSN: 0033-7587
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The radiosensitization of hypoxic Chinese hamster ovary (HA-1) cells in vitro by misonidazole (MIS) and other 1-substituted 2-nitroimidazoles depends on the rate and extent of intracellular uptake of these radiosensitizers, which in turn is governed by their lipophilicity [expressed as the octanol:water partition coeff. (P)]. As the lipophilicity of the compds. decreased, the rate of drug entry into the cells was slower, and below P values of .apprx.0.05, peak intracellular drug concns. were lower than that of MIS (P = 0.43). In addn., the no. of hydroxyl groups on the side chain of the nitroimidazole mol. influenced the uptake of drug into the cells. For compds. of similar P, but differing in the no. of side-chain hydroxyl groups, the addn. of a single hydroxyl group to the mol. decreased the amt. of drug entering the cell by a factor of .apprx.2. These compds. enter the cell by nonmediated passive diffusion since altering the energy (ATP) capacity of the cell by 2-deoxyglucose did not affect uptake. Increases in temp. or decreases in pH can increase the intracellular uptake of MIS. For example, equal intracellular and extracellular concns. (100% uptake) of MIS were obtained if cells were heated to 44-45.degree. for 15 min compared to 20-40% uptake at 37.degree.. Increases in MIS uptake by factors of 2-3 could be demonstrated within 30 min when cells were incubated in Hanks' balanced salt soln. at pH 6.0-6.3 without loss of cell viability. In addn., MIS uptake in aerobic cultured cells varied 15-60%, depending on the cell line and culture conditions used.
IT **74141-75-6**
RL: BIOL (Biological study)
(metab. of and radiosensitization by, of CHO cells in vitro)
RN 74141-75-6 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)

L11 ANSWER 53 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



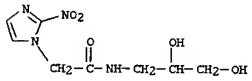
L11 ANSWER 54 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:83220 CAPLUS
DOCUMENT NUMBER: 98:83220
TITLE: Structure/activity relationships for the enhancement by electron-affinic drugs of the anti-tumor effect of CCNU
AUTHOR(S): Workman, P.; Twentyman, P. R.
CORPORATE SOURCE: MRC Clin. Oncol. Radiother. Unit, MRC Cent., Cambridge, CB2 2H, UK
SOURCE: British Journal of Cancer (1982), 46(2), 249-59
CODEN: BJCAAI; ISSN: 0007-0920
DOCUMENT TYPE: Journal
LANGUAGE: English
AB By means of a regrowth-delay assay, structure/activity relations for the enhancement by electron-affinic agents of the antitumor effect of the nitrosourea CCNU [13010-47-4] against the KHT sarcoma in C3H mice were investigated. A series of neutral 2-nitroimidazoles similar in electron affinity but varying in octanol/water partition coeff. (PC) over 4 orders of magnitude were examd. at a fixed dose of 2.5 mmol/kg. A parabolic (quadratic) dependence of activity on log PC was obsd. Analogs more hydrophilic than misonidazole (MISO) [13551-87-6] were inactive, as were those with very high PCs (>20). Those with PC 0.43-20 were usually more active than MISO. The fairly lipophilic 5-nitroimidazoles nimorazole [6506-37-2] and metronidazole (METRO) [443-48-1] had activity similar to that of MISO, despite their reduced electron affinity. Two basic 2-nitroimidazoles more efficient as radiosensitizers in vitro likewise showed activity comparable to MISO. Several agents more electron-affinic than MISO, including some nonnitro compds., were also investigated. Most of these agents were inactive at max. tolerated doses, but nitrofurazone [59-87-0] showed reasonable activity. Sensitizer dose-response curves were obtained for MISO, METRO, and two of the most effective agents, benznidazole [22994-85-0] and Ro 07-1902 [68160-71-4]. The latter 2 agents were both considerably more active than MISO at low doses (0.1-0.9 mmol/kg). Apparently, the structural features of electron-affinic agents responsible for the enhancement of KHT tumor response to CCNU are quite different from these affecting radiosensitization, lipophilicity being particularly important. The microsomal enzyme inhibitor SKF 525A [62-68-0] increased the antitumor effect of CCNU, suggesting inhibition of CCNU metab. as 1 possible mechanism contributing to chemosensitization by lipophilic electron-affinic agents in mice.

L11 ANSWER 54 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
IT **74141-75-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(antitumor activity of CCNU response to, structure in relation to)
RN 74141-75-6 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)

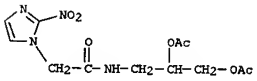


L11 ANSWER 55 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1982:213378 CAPLUS
DOCUMENT NUMBER: 96:213378
TITLE: Structure-activity relationships of 1-substituted 2-nitroimidazoles: effect of partition coefficient and side-chain hydroxyl groups on radiosensitization in vitro
AUTHOR(S): Brown, D. M.; Parker, E.; Brown, J. M.
CORPORATE SOURCE: Sch. Med., Stanford Univ., Stanford, CA, 94305, USA
SOURCE: Radiation Research (1982), 90(1), 98-108
CODEN: RAREAE; ISSN: 0033-7587
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fourteen 1-substituted 2-nitroimidazoles that ranged in lipophilicity with partition coeffs. (P) of 0.014-2.75 and that varied in the no. of OH groups (0-3) on the side chain at the 1-position of the nitroimidazole ring were studied for their ability to radiosensitize hypoxic Chinese hamster ovary cells (HA-1) in vitro. The concn. (C1.6) of each compd. required for achieving an enhancement ratio (ER) of 1.6 was plotted as a function of P. Multiple linear regression analyses were performed to det. the influence of P and the no. of OH groups according to the equation -log C1.6 = b0 + b1 log P + b2 (log P)2 + b3 (OH). Either independent variable log P or (log P)2 was significantly nonzero, and, if used sep. in the equation without the OH group term, could account for 51% of the explained variance (r2) in the fit of the data. The no. of OH groups on the side chain affected radiosensitization or to a greater extent than P in the range presently studied (r2 for the OH term alone was 0.58). An increase in OH group no. by 1 with no change in lipophilicity resulted in an increase in drug concn. needed for the equiv. radiosensitization by a factor of 2. The use of either the log P or (log P)2 terms together with the OH group term increased the r2 value to 0.70. These data are relevant to the development of radiosensitizers potentially superior to misonidazole for clin. use, since they show that lipophilicity can only be decreased to .apprx.10% of that of misonidazole without producing a loss of radiosensitizing effectiveness, and that independent of lipophilicity, the addn. of OH groups to the mol. also reduces the radiosensitizing effectiveness.
IT **74141-75-6 81892-65-1 81892-66-2 81892-68-4**
RL: BIOL (Biological study)
(radiosensitization by, structure in relation to)

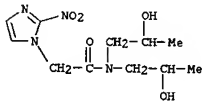
L11 ANSWER 55 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
RN 74141-75-6 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)



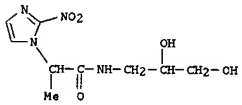
RN 81892-65-1 CAPLUS
CN 1H-Imidazole-1-acetamide, N-[2,3-bis(acetyloxy)propyl]-2-nitro- (9CI) (CA INDEX NAME)



RN 81892-66-2 CAPLUS
CN 1H-Imidazole-1-acetamide, N,N-bis(2-hydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)



RN 81892-68-4 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-.alpha.-methyl-2-nitro- (9CI) (CA INDEX NAME)



L11 ANSWER 55 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

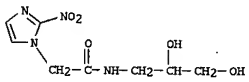
L11 ANSWER 56 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1982:42966 CAPLUS
DOCUMENT NUMBER: 96:42966
TITLE: Polarographic analysis of heterocyclic nitrogen compounds
AUTHOR(S): Leach, Steven C.; Weaver, Robert D.; Kinoshita, Kimio; Lee, William W.
CORPORATE SOURCE: SRI Int., Menlo Park, CA, 94025, USA
SOURCE: Journal of Electroanalytical Chemistry and Interfacial Electrochemistry (1981), 129(1-2), 213-27
CODEN: JEIEBC; ISSN: 0022-0728
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A correlation between the redn. potential of heterocyclic compds. and their effectiveness as radiosensitizing agents in cancer therapy has been reported. This correlation provides a guide for evaluating the effectiveness of newly synthesized compds. as radiosensitizers. The half-wave redn. potential (E1/2) of selected nitroimidazoles, nitrotriazoles and heterocyclic amine N-oxides was measured at a dropping Hg electrode in a Britton-Robinson buffer, pH 7.4. The effect of various substituent groups on the half-wave redn. potential of the heterocyclic compds. was investigated and the results are compared with published data. A single redn. wave was obsd. with the nitroimidiazoles and nitrotriazoles, whereas multiple redn. waves were obsd. with several of the N-oxides of pyridine, quinoxaline and phenazine. When electron-attracting substituents were attached to the heterocyclic ring on nitroimidazole and nitrotriazole, the redn. of the nitro group was easier and E1/2 shifted in the pos. direction relative to that of the parent compd.

IT **74141-75-6**
RL: PRP (Properties)
(neoplasm inhibitor, for carcinoma, elec. redn. potential in relation to)

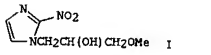
RN 74141-75-6 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)



L11 ANSWER 56 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

L11 ANSWER 57 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1981:473052 CAPLUS
DOCUMENT NUMBER: 95:73052
TITLE: Pharmacokinetic considerations in radiosensitizer development
AUTHOR(S): Brown, J. Martin; Lee, William W.
CORPORATE SOURCE: Sch. Med., Stanford Univ., Stanford, CA, USA
SOURCE: Radiat. Sensitizers: Their Use Clin. Manage. Cancer, [Proc. Conf.] (1980), Meeting Date 1979, 2-13. Editor(s): Brady, Luther W. Masson USA: New York, N. Y.
CODEN: 45OJAG
DOCUMENT TYPE: Conference
LANGUAGE: English
GI



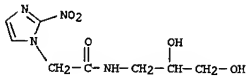
I

AB Tissue distribution and pharmacokinetic studies on 10 nitroimidazole radiosensitizers showed that there are compds. which have the same electron affinity and the same ability to radiosensitize hypoxic tumor cells in vivo as misonidazole (I) [13551-87-6], but are less toxic to mice. This reduced toxicity was correlated with a decreased ability of the compds. with a decreased ability of the compds. to cross the blood-brain barrier indicating these drugs to be less neurotoxic than I. While the lipophilicity and partition coeff. of these drugs reflected their ability to permeate the blood-brain barrier, the tumor-plasma ratio was largely independent of the lipid soly.-or the partition coeff. The concn. of SR-2555 [74141-74-5], a hydrophilic drug, in the hypoxic cells was as good as that of I. Thus, the main disadvantage of these agents compared to I was poor absorption after i.p. and oral administration.

IT **74141-75-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(radiosensitizing activity of, pharmacokinetics in relation to)

RN 74141-75-6 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)

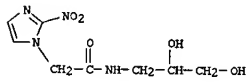
L11 ANSWER 57 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



L11 ANSWER 58 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:150996 CAPLUS
DOCUMENT NUMBER: 94:150996
TITLE: Radiosensitization of hypoxic bacterial cells by nitroimidazoles of low lipophilicity: steady-state and rapid-mix studies
AUTHOR(S): Anderson, Robert F.; Patel, Kantilal B.; Sehmi, Darshan S.
CORPORATE SOURCE: Cancer Res. Campaign Gray Lab., Mount Vernon Hosp., Middlesex, HA6 2RN, UK
SOURCE: Radiation Research (1981), 85(3), 496-504
CODEN: RAREAE; ISSN: 0033-7587
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Radiosensitization of hypoxic bacterial cells by five 2-nitroimidazoles, with similar redn. potentials to misonidazole [13551-87-6] but having lower lipophilicities, has been measured in Escherichia coli AB 1157 and Streptococcus lactis 712. Sensitization efficiency progressively decreased with decreasing lipophilicity in E. coli but no in S. lactis. This difference is discussed in terms of the differing membrane properties of the 2 bacteria; E. coli resembled a multicompartment model, as would also be expected with mammalian cells. Rapid-mix expts. are described which show that the radiosensitization obsd. after preirradn. contact times during .apprx.3-30 ms is dependent on the lipophilicity of the sensitizer, higher lipophilicity resulting in a lower contact time being required for radiosensitization. This result and the observation that a highly lipophilic compd. affects only half the full O enhancement level after short contact times suggest that part of the sensitization process occurs in a lipophilic (membrane) compartment of the cell.

IT **74141-75-6**
RL: PRP (Properties)
(radiosensitization by, of bacteria, lipophilicity in relation to)
RN 74141-75-6 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)



L11 ANSWER 58 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

L11 ANSWER 59 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1980:461024 CAPLUS
DOCUMENT NUMBER: 93:61024
TITLE: Partition coefficient as a guide to the development of radiosensitizers which are less toxic than misonidazole
AUTHOR(S): Brown, J. Martin; Workman, Paul
CORPORATE SOURCE: Clin. Oncol. Radiotherapeut. Unit, MRC, Cambridge, UK
SOURCE: Radiation Research (1980), 82(1), 171-90
CODEN: RAREAE; ISSN: 0033-7587
DOCUMENT TYPE: Journal
LANGUAGE: English
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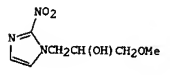
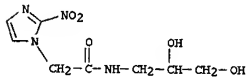


I

AB Ten 2-nitroimidazole radiosensitizers of electron affinity equal to that of misonidazole (I), but differing in their octanol:water partition coeff. (P) over a 100-fold range, were chosen to examine the effect of lipophilicity on the pharmacokinetics of these drugs in BALB/c mice bearing EMT6 tumors. Plasma, tumor, and brain concns. were assayed as a function of time after a single i.p. injection of each drug. Peak concns. in the tumor declined with decreasing lipophilicity (decreasing P), but this was due to declining peak plasma concns. resulting from slower drug absorption and could be overcome by i.v. injection. The tumor/plasma ratio, once sufficient time had elapsed for it to reach its equil. value, was independent of P over the range 0.026-1.5 but showed a 50% redn. in this ratio for the most hydrophilic compd. studied (P = 0.014). This compd. was also the one drug in the series which was significantly poorer than I in its radiosensitization as a function of drug concn. The brain/plasma ratio, on the other hand, showed a marked dependence on lipophilicity. For I and more lipophilic compds., the brain/plasma ratio was 1.0, but as the lipophilicity decreased below that of I, the compds. showed an increasing difficulty in penetration into the brain, and brain/plasma ratios correlated with an increased acute LD50 of the drugs.

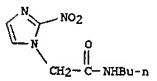
L11 ANSWER 59 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
Bilateral nephrectomy was used to increase the apparent plasma half-life of SR-2508 [22668-01-5] from 0.8 to 15 h. This change, however, did not affect the tumor-brain ratio of .apprx.10 for this drug. These pharmacokinetic data are discussed in terms of the development of a radiosensitizer superior to I for clin. use.

IT **74141-75-6**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(pharmacokinetics and toxicity of, partition coeffs. in relation to)
RN 74141-75-6 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)



L11 ANSWER 60 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1969:422065 CAPLUS
DOCUMENT NUMBER: 71:22065
TITLE: Studies in the nitroimidazole series. III. 2-Nitroimidazole derivatives substituted in the 1-position
AUTHOR(S): Beaman, Alden G.; Tautz, William; Duschinsky, Robert
CORPORATE SOURCE: Chem. Res. Dep., Hoffmann-La Roche, Inc., Nutley, NJ, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1961-70) (1968), Volume Date 1967 520-30
CODEN: AACHAX; ISSN: 0074-9923
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB Derivs. of 2-nitroimidazole (I), which is active against Trichomonas infections, are prepd. Of the prepd. derivs., those with a substituted 2-propanol group in the 1 position exhibited the best activity against Trichomonas vaginalis in mice. These compds. were prepd. by the reaction of I with the appropriate 1,2-epoxy-3-substituted propane in refluxing water, EtOH, or excess propane deriv. in the presence of K2CO3, NaOH, or aq. NH3. II prepd. in this manner were (R, m.p., and % yield given): OH, 110-12.degree., 43; Cl (III), 156-8.degree., 78; MeO (IV) 110-11.degree., 72; PhO, 142.5-3.5.degree., 60; 2,4-Cl2C6H3O, 160-2.degree., 64; PrO, 74.5-6.0.degree., 20; allyloxy (V) 57.5-8.5.degree., 46. Similarly 4,5-dimethyl-2-nitroimidazole with epichlorohydrin and 1,2-epoxy-3-methoxy-2-propanol gave 43% 1-(4,5-dimethyl-2-nitro-1-imidazolyl)-3-chloro-2-propanol, m. 165.5-6.5.degree., and 54% 1-(4,5-dimethyl-2-nitro-1-imidazolyl)-3-methoxy-2-propanol, m. 120-1.degree., resp. Other active compds. against Trichomonas infections were amide derivs. of 2-nitroimidazole-1-alkanoic acids. Some of these amides were prepd. by the reaction of the Na salt of I with an alkyl .omega.-haloalkanoate in HCONMe2 at 100-150.degree. followed by reaction with an amine in MeOH at 25.degree.. VI prepd. by this method were (n, R, R1, m.p. and % yield given): 1, H, Bu, 124-5.degree., 82; 1, H, MeCH(OH)CH2, 162-3.degree., 75; 1, Me, Me, 129-130.degree., 81; 1, H, 3,4-(MeO)2-C6H3CH2CH2, 150.5-1.0.degree., 89; 1, H, 2-pyridylmethyl, 162.5-3.5.degree., 72; 1, H, 4-amino-2-methylpyrimidin-5-ylmethyl, 299-300.degree. (decompn.), 58; 3, Me, Me, 88-9.degree., 27. Similarly prepd. were: 62% N-iso-Pr, m. 153-4.degree., and 83% N-benzyl, m. 151.0-1.5.degree., derivs. of 2-hydroxy-3-(2-nitroimidazol-1-yl)propionamide. Several other amides are prepd. by a more general method

L11 ANSWER 60 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
in which an N-substituted or N,N-disubstituted .omega.-haloalkanoic acid amide is prepd. in H2O at 0.degree. from an .omega.-haloalkanoic acid chloride and an amine and is treated with the Na salt of I in HCONMe2 at 100-150.degree.. VI (n = 1, R1 = H) prepd. by this method were (R, m.p. and % yield given): H, 102.0-3.5.degree., 69; Me, 174-5.degree., 87; p-MeOC6H4, 207.0-7.5.degree., 66; o-O2NC6H4CH2, - (2 forms m. 166.5-8.5.degree. and 175.5-6.5.degree.), 68. Lower activity and usually higher toxicity were exhibited by 1-(substituted benzyl) derivs. of I prepd. from the Na salt of I and a benzyl halide. These compds. were: 83% 1-(p-nitrobenzyl)-2-nitroimidazole, m. 130.0-1.5.degree., and 46% 1-(p-chlorobenzyl)-2-nitroimidazole, m. 108.0-9.5.degree.. The following preprns. of various derivs. of the above compds. are also described. III was treated with NaOH to prep. 89% 1-(2,3-epoxypropyl)-2-nitroimidazole, m. 53.5-5.0.degree.. IV treated with CrO3 gave 67% 1-(2-nitro-1-imidazolyl)-3-methoxy-2-propanone, m. 65-6.degree.; semicarbazone m. 181-3.degree.. III was also converted to its anisate (m. 73-5.degree., 69% yield) and its acetate (m. 62-4.degree., 41% yield) by the usual methods. IV was treated with Br to give 1-(2-nitro-1-imidazolyl)-3-(2,3-dibromopropoxy)-2-propanol, m. 71-3.degree.. I treated with NaOMe and ClCH2CO2Me or Cl(CH2)3CO2Me gave 91% Me (2-nitro-1-imidazolyl)acetate, m. 94-5.degree., and the corresponding butyrate. N-(o-Nitrobenzyl)chloroacetamide (m. 92.5-4.5.degree., 30% yield) was prepd. from o-nitrobenzylamine-HCl and ClCH2COCl. A mixt. of I, K2CO3, EtOH, and Et glycidate was refluxed to prep. 87% Et 3-(2-nitro-1-imidazolyl)lactate, m. 147.0-8.5.degree.. N-Methyl-(4,5-dimethyl-2-nitro-1-imidazolyl)acetamide (m. 170-2.degree., 27% yield) was prepd. by treatment of 4,5-dimethyl-2-nitroimidazole with NaOMe and ClCH2CONHMe.
IT 22668-00-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 22668-00-4 CAPLUS
CN 1H-Imidazole-1-acetamide, N-butyl-2-nitro- (9CI) (CA INDEX NAME)



L11 ANSWER 60 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

L11 ANSWER 61 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1969:403383 CAPLUS
DOCUMENT NUMBER: 71:3383
TITLE: Biocidal (2-nitroimidazolyl) alkanoic acids and derivatives
PATENT ASSIGNEE(S): Hoffmann-La Roche, F., und Co., A.-G.
SOURCE: Brit., 20 pp.
CODEN: BRXXAA
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 1138529		19690101		
PRIORITY APPLN. INFO.:			US	19660418

AB The title compds. are prepd. Thus, to a slurry of 100 g. powd. sublimed 2-nitroimidazole (I) in 500 ml. HCONMe2 is added 200 ml. 4.44N NaOMe in MeOH, followed by just sufficient I to change the color of the soln. from pink to yellow, the soln. heated at 153.degree. to remove MeOH, cooled to 90.degree., 135 ml. ClCH2CO2Me added (the temp. first rising spontaneously to 122.degree. and then falling), the mixt. heated 15 min. at 105-115.degree. and worked up to give 12 g. Me ester (II) of (2-nitroimidazolyl)acetic acid (III), pale yellow, m. 94-5.degree. (EtOH). Similarly prepd. are the Et ester of 3-(2-nitroimidazolyl)propionic acid (IV), m. 47.5-49.degree. (CCl4), methyl 4-(2-nitroimidazolyl)butyrate and methyl 5-(2-nitroimidazolyl)valerate. A soln. of 20 g. II in 1200 ml. 0.1N NaOH is refluxed 15 min., cooled, acidified (pH 1.7) with 120 ml. N HCl, and extd. with 3 .times. 100 ml. EtOAc to give III, m. 159-60.degree. (explodes; decompn. point depends on heating rate). HOCH2CH2NH2 (10 ml.) is added to a stirred slurry of 10 g. II in 50 ml. abs. EtOH the mixt. kept 18 hrs. at room temp. (solid began forming after 15 min.), cooled 7 hrs. in the freezer, the solid filtered off, washed with 2 .times. 10 ml. abs. MeOH, and dried to give III 2-hydroxyethylamide, m. 162-3.degree. (abs. EtOH). Similarly prepd. are the following amides of III (R in CONHR and m.p. given): PhCH2, 188.5-90.degree.; MeO(CH2)3, 118-19.degree. (EtOAc); furfuryl, 179-80.degree.; NHR = morpholino, 113.5-15.degree.; NHR = piperidino, 102-3.5.degree. (EtOAc); 2-ClC6H4CH2, 208-9.degree.; 3-pyridyl, 194-5.5.degree.; 2-pyridyl, 162.5-3.5.degree. (H2O); H2NCH2CH2, 189-90.degree. (decompn.); 3,4-(MeO)2C6H3CH2CH2, 150.5-1.degree.;

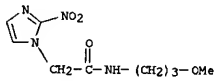
L11 ANSWER 61 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
2-O2NC6H4CH2 (V), 175.5-6.5.degree.; 4-MeOC6H4CH2, 211-11.5.degree.; 5-(2-methyl-4-aminopyrimidinyl)methyl, 299-300.degree. (decompn.) (H2O);
2-imidazolyl, 241-2.degree. (decompn.) (H2O); 4-H2NC6H4-CH2, 208-9.degree.. Also prepd. are R(CH2)nCONR1R2 (VI)(R is 2-nitroimidazolyl) (n, R1, R2, and m.p. given: 3, Me, H, 125-6.degree.; 3, Me, Me (VII), 88-9.degree.; 3, Me2CHCH2, H, 79.5-81.5.degree.; 4, Me, H, 94.5-6.5.degree. (25:2 benzene-EtOH); 4, Me, Me, 85.5-7.degree. (CCl4). A soln. of 3.11 g. I in 30 ml. HCONMe2 and 6.09 ml. 4.52N NaOMe in MeOH is heated to 152.degree., cooled to 110.degree., 6.35 g. ClCH2CONHC6H4NO2-2 added, the mixt. heated 30 min. at 100-120.degree., concd. at 60.degree. in vacuo, the residual oil dissolved in 25 ml. abs. EtOH, and kept over the weekend to give V, m. 166.5-8.5.degree. (EtOH); similarly prepd. is III 4-anisidide, m. 207-7.5.degree. (EtOH). A soln. of 13.4 g. NaOH in 120 ml. distd. H2O is cooled to 0.degree., 24.1 g. Me2CHNH2 added, the soln. cooled to 0.degree., 26 g. Cl(CH2)2COCl added dropwise with vigorous stirring at 0-8.degree., and the mixt. stirred a further 10 min. to give Cl(CH2)2CONHCMe2 (VIII), m. 69-70.5.degree. (H2O). Similarly prepd. are the following X(CH2)nCONR1R2 (X, n, R1, and R2 given): Cl, 3, Me, Me, (oil); Cl, 3, Me2CH, H (m. 52-4.degree.); cl, 3, Ph-CH2, H (m. 66-7.5.degree.); Cl, 4, Me2CH, H (oil); Br, 5, Me2CH, H (solid); Br, 5, Me, H (oil); Br, 5, Me, Me (oil); Br, 5, PhCH2, H [m. 55-7.degree. (Et2O)]. I (2.22 g.) is dissolved in 4.3 ml. 4.56N NaOMe in MeOH, a pinch of I added to change the color of soln. from orange to yellow, 20 ml. HCONMe2 are added, the soln. heated to 152.degree., cooled to 110.degree., 3.12 g. VIII added, the mixt. stirred 4 hrs. at 110-130.degree., and worked up to give IV isopropylamide, m. 117-18.degree. (abs. EtOH). Similarly prepd. are VI (n, R1, R2, and m.p. given): 3, Me2CH, H, 103-3.5.degree.; 3, PhCH2, H, 89.5-90.degree.; 4, Me2CH, H, 83-3.5.degree. (CHCl3-CCl4); 5, Me2CH, H, 87-8.degree. (distd. H2O); 5, Me, H, 95-7.degree.; 5, Me, Me, 73.5-5.5.degree.,5, PhCH2, H, 103-4.5.degree.; and VII, m. 86-7.5.degree.. A mixt. of 10 g. powd. and sieved sublimed I, 1 g. anhyd. K2CO3, 100 ml. abs. EtOH and 20.78 g. Et glycidate (d. 1.093, b. 77-9.degree./34 mm.) is refluxed with stirring until the uv spectrum in 0.1N base had a max. at 327 m.mu., and no shoulder at 375 m.mu. (.apprx.40

L11 ANSWER 61 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
mins.), filtered and the filtrate refrigerated .apprx.2 hrs. to give the Et ester (IX) of 3-(2-nitroimidazolyl)lactic acid (X), m. 147-8.5.degree. (EtOH). IX (1.4 g.) is added to a stirred soln. of 5 ml. PhCH2NH2 in 27 ml. abs. MeOH, the soln. stirred overnight at room temp., allowed to evap. gave X benzylamide, m. 151-1.5.degree. (EtOH). Similarly prepd. are amides of X. (R in COHR and m.p. given): 3-MeO(CH2)3, 111-12.degree., (NHR)piperidino, 131-2.degree.; Me2CHCH2, 136-7.degree., Me, 129-32.degree.; Me2CH, 152.5-3.degree., (nHR =)NMe2, 130-1.5.degree.. A soln. of 2.39 g. 4,5-dimethyl-2-nitroimidazole in 4 ml. 4.44N methanolic NaOMe is evapd. in vacuo, the residual solid and 2.38 g. ClCH2CONHMe dissolved in 25 ml. HCONMe2, refluxed 15 min., the solvent removed in vacuo and the residue worked up to give N-methyl-2-(4,5-dimethyl-2-nitroimidazolyl)-acetamide, m. 170-2.degree. (CHCl3). The title compds. are active against bacteria, pathogenic yeasts, and protozoa, and are useful in treating diseases caused by Trichomonas vaginalis, T. foetus, Histomonas meleogridis, Trypanosoma cruzi, Trypanosoma rhodesiense, and Trypanosoma congolense. 5 examples of pharmaceutical formulations are provided.

IT **22813-34-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

RN 22813-34-9 CAPLUS

CN Imidazole-1-acetamide, N-(3-methoxypropyl)-2-nitro- (8CI) (CA INDEX NAME)



L11 ANSWER 62 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1969:10175 CAPLUS
DOCUMENT NUMBER: 70:10175
TITLE: Antiprotozoan and antibacterial activity of 2-nitroimidazole derivatives
AUTHOR(S): Grunberg, Emanuel; Beskid, G.; Cleeland, R.; DeLorenzo, W. F.; Titsworth, E.; Scholer, H. J.; Richle, R.; Brener, Z.
CORPORATE SOURCE: Dep. of Chemother., Hoffmann-La Roche, Inc., Nutley, NJ, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1961-70) (1968), Volume Date 1967 513-19
CODEN: AACHAX; ISSN: 0074-9923
DOCUMENT TYPE: Journal
LANGUAGE: English

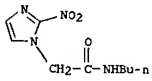
AB Three propanols [1-(2-nitro-1-imidazolyl)-3-methoxy-2-propanol (I); 3-(2-nitro-1-imidazolyl)-1,2-propanediol (II); 1-(2-nitro-1-imidazolyl)-3-allyloxy-2-propanol (III)], 4 amides [N-butyl-2-nitro-1-imidazoleacetamide (IV); N-(2-hydroxyethyl)-2-nitro-1-imidazoleacetamide (V); N,N-dimethyl-2-nitro-1-imidazolebutyramide (VI); N,N-dimethyl-2-nitro-1-imidazoleacetamide (VII)], and one benzyl deriv. [1-p-nitrobenzyl-2-nitroimidazole (VIII)] all exhibited low-to-moderate degrees to acute toxicity in mice. All but V, as judged by the 50% curative dose, showed moderate-to-marked activity against Trichomonas vaginalis and Trichomonas foetus infections in mice when administered orally, and against the local T. vaginalis infection when given s.c. I and VIII were moderately active against Entamoeba histolytica in the intracecal infection of rats. I was also effective both orally and s.c. against a hepatic infection of hamsters due to E. histolytica. All were inactive against Trypanosoma brucei and Trypanosoma equiperdum infections in mice. I, III, and VIII exhbited a slight effect against Trypanosoma cruzi, i.e., a delay of 4-7 days in the emergence of trypanosomes in treated animals, as compared to untreated controls. II was highly active both prophylactically and therapeutically against T. cruzi. None showed activity, either orally or s.c. against lethal systemic infections of mice due to Pseudomonas aeruginosa or Proteus vulgaris. V and VIII exhibited at slight-to-moderate effect against Streptococcus pyogenes, while slight-to-marked activity against Escherichia coli was noted with III, V, VI, and VIII when the drugs were given orally or s.c. The most consistent antibacterial activity observed was against Staphylococcus aureus; I, II,

L11 ANSWER 62 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
III, V, VI and VII showed activity ranging from slight to marked when administered orally, s.c., or by both routes.

IT **22668-00-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bactericidal activity of)

RN 22668-00-4 CAPLUS

CN 1H-Imidazole-1-acetamide, N-butyl-2-nitro- (9CI) (CA INDEX NAME)



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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-40.36	-40.36

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Executing the logoff script...

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